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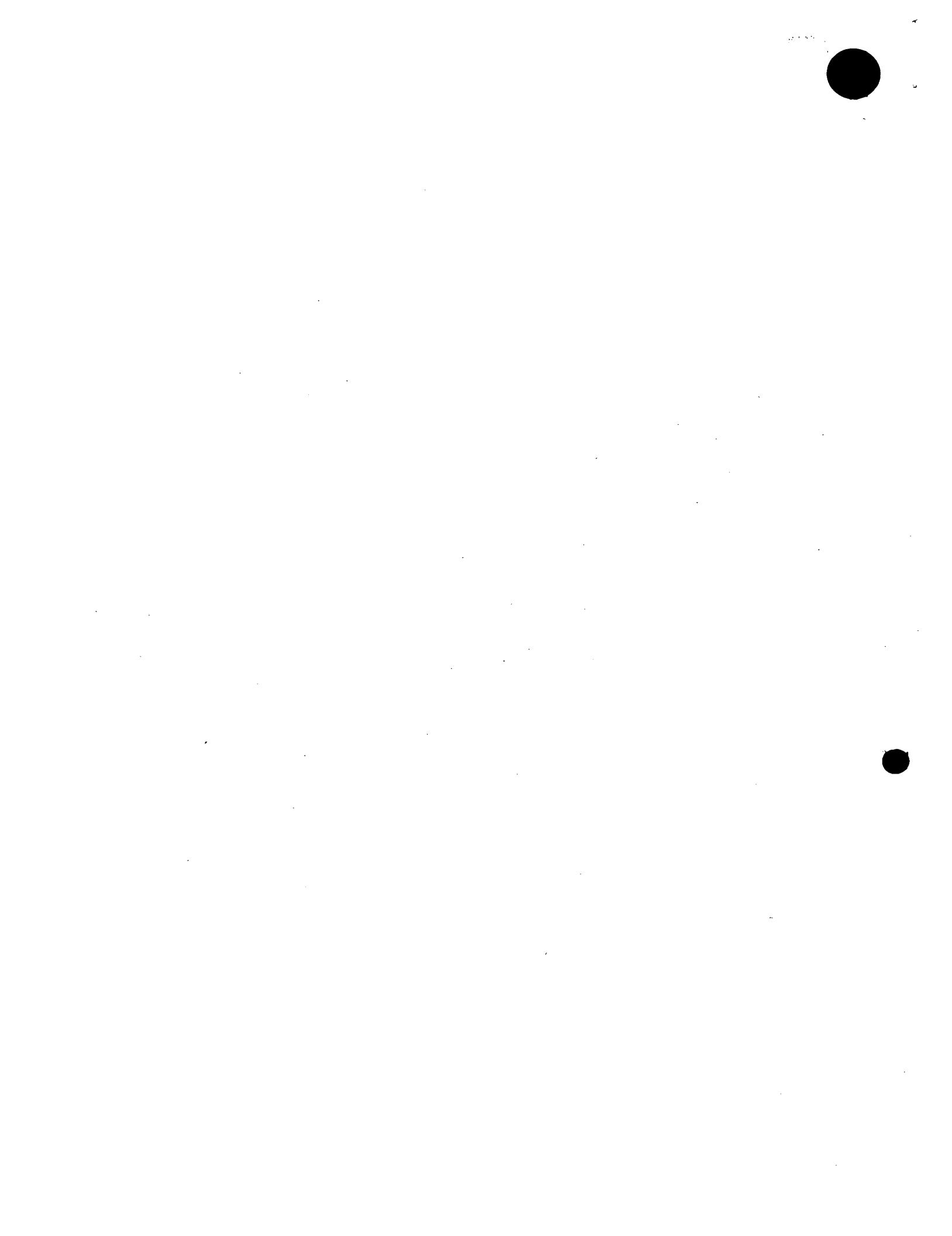
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1/77

Request for grant of a patent

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1. Your Reference	MJS/DMK/PI3806		
2. Pa (Th)	9923748.9 -7 OCT 1999		
3. Full name, address and postcode of the or of each applicant (underline all surnames)	GLAXO GROUP LIMITED GLAXO WELLCOME HOUSE BERKELEY AVENUE GREENFORD MIDDLESEX UB6 0NN GB		
Patents ADP number (if you know it)	<i>473587003</i>		
If the applicant is a corporate body, give the country/state of its corporation	GB		
4 Title of the invention	CHEMICAL COMPOUNDS		
5 Name of your agent (if you know one)	MICHAEL J STOTT (SEE CONTINUATION SHEET)		
"Address for service" in the United Kingdom to which all correspondence should be sent (including the postcode)	GLAXO WELLCOME PLC GLAXO WELLCOME HOUSE, BERKELEY AVENUE GREENFORD, MIDDLESEX UB6 0NN, GB		
Patents ADP number (if you know it)	<i>13315-75003</i>		
6. If you are declaring priority from one or more earlier patent applications, give the country and date of filing of the or of each of these earlier applications and (if you know it) the or each application number	Country	Priority application number (if you know it)	Date of Filing (day / month / year)
7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application	Number of earlier application		Date of filing (day / month / year)
8. Is a statement of inventorship and of right to grant a patent required in support of this request? (Answer yes if: a) any applicant named in part 3 is not an inventor, or b) there is an inventor who is not named as an applicant, or c) any named applicant is a corporate body.	YES		

See note (d))

Patents Form 1/77

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Continuation sheets of this form	1
Description	61
Claim(s)	3
Abstract	2
Drawing(s)	-

10. If you are also filing any of the following,

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Priority Documents**Translations of priority documents**

Statement of inventorship and right
to grant of a patent (*Patents Form 7/77*)

Request for preliminary examination
and search (*Patent Form 9/77*)

Request for substantive examination
(*Patent Form 10/77*)

Any other documents
(please specify)

11. **I/We request the grant of a patent on the basis of this application**

Signature MICHAEL J STOTT 07 October 1999
AGENT FOR THE APPLICANTS

12. Name and daytime telephone number of
person to contact in the United Kingdom

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(See Page 1 No. 5)

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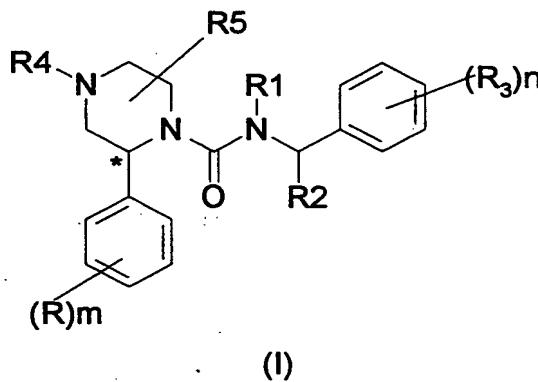
Chemical Compounds

The present invention relates to piperazine derivatives, to processes for their preparation, to pharmaceutical compositions containing them and to their medical use.

In particular the invention relates to novel compounds which are potent and specific antagonists of tachykinins, including substance P and other neurokinins.

10

The present invention provides compounds of formula (I)



15

wherein

R represents a halogen atom or a C₁₋₄ alkyl group;

R₁ represents hydrogen or a C₁₋₄ alkyl group;

R₂ represents hydrogen or a C₁₋₄ alkyl group;

R₃ represents a trifluoromethyl, a C₁₋₄ alkyl, a C₁₋₄ alkoxy, a trifluoromethoxy or a halogen group;

R₄ represents hydrogen, a (CH₂)_qR₇ or a (CH₂)_rCO(CH₂)_pR₇ group;

R₅ represents hydrogen, a C₁₋₄ alkyl or a COR₆ group;

R₆ represents hydrogen, hydroxy, amino, methylamino, dimethylamino, a 5 membered heteroaryl group containing 1 to 3 heteroatoms selected from oxygen, sulphur and nitrogen or a 6 membered heteroaryl group containing 1 to 3 nitrogen atoms;

R₇ represents hydrogen, hydroxy, a saturated 5-7 membered heterocyclic group, a 5 membered heteroaryl group containing 1 to 3 heteroatoms selected from oxygen, sulphur and nitrogen, a 6 membered heteroaryl group containing 1 to 3 nitrogen atoms or NR₈R₉ wherein R₈

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and R₉ represent independently hydrogen or C₁₋₄ alkyl optionally substituted by a hydroxy, amino, by a 5 membered heteroaryl group containing 1 to 3 heteroatoms selected from oxygen, sulphur and nitrogen, by a 6 membered heteroaryl group containing 1 to 3 nitrogen atoms or saturated 5-7 membered heterocyclic or R₈ and R₉ together with the nitrogen atom to which they are attached represent a saturated 5-7 membered heterocyclic group optionally containing an additional heteroatom selected from oxygen, sulphur or nitrogen;

5 m is zero or an integer from 1 to 3; n is zero or an integer from 1 to 3; p or r are zero or an integer from 1 to 4; q is an integer from 1 to 4 and

10 pharmaceutically acceptable salts and solvates thereof.

Suitable pharmaceutically acceptable salts of the compounds of general formula (I) include acid addition salts formed with pharmaceutically acceptable organic or inorganic acids, for example hydrochlorides, hydrobromides, sulphates, alkyl- or arylsulphonates (e.g. methanesulphonates or p-toluenesulphonates), phosphates, acetates, citrates, succinates, tartrates, fumarates and maleates.

20 The solvates may, for example, be hydrates.

References hereinafter to a compound according to the invention include both compounds of formula (I) and their pharmaceutically acceptable acid addition salts together with pharmaceutically acceptable solvates.

25 It will be appreciated by those skilled in the art that the compounds of formula (I) contain at least one chiral centre (namely the carbon atom shown as * in formula (I)).

Thus, when R₂ is a C₁₋₄ alkyl or a trifluoromethyl group and R₅ is hydrogen, the compounds of formula (I) possess two asymmetric carbon atoms. Furthermore, when R₂ is a C₁₋₄ alkyl or a trifluoromethyl group and R₅ is a C₁₋₄ alkyl or a COR₆ group, the compounds of the invention possess three asymmetric carbon atoms. It is to be understood that all enantiomers and diastereomers and mixtures thereof are encompassed within the scope of the present invention.

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The term alkyl as used herein as a group or a part of the group refers to a straight or branched alkyl group containing from 1 to 4 carbon atoms; examples of such groups include methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl, or tert butyl.

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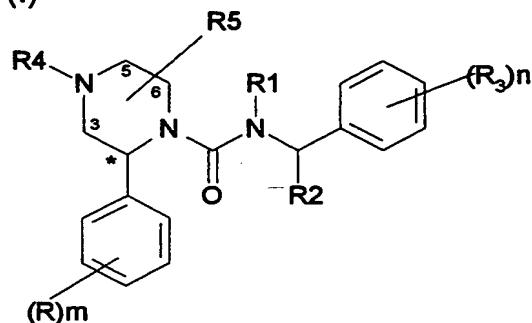
The term halogen refers to a fluorine, chlorine, bromine or iodine atom.

The term C₁₋₄ alkoxy group may be a straight chain or a branched chain alkoxy group, for example methoxy, ethoxy, propoxy, pro-2-oxy, butoxy, but-2-oxy or methylpro-2-oxy.

When R₆ or R₇ are a 5 or 6 membered heteroaryl group or when R₈ or R₉ are C₁₋₄ alkyl optionally substituted by a 5 or 6 membered heteroaryl group, according to the invention they include furanyl, thiophenyl, imidazolyl, thiazolyl, oxazolyl, pyridyl or pyrimidinyl.

When R₇ is a saturated 5-7 membered heterocyclic group or when R₈ or R₉ are C₁₋₄ alkyl optionally substituted by a 5-7 membered heterocyclic group, this may be for example morpholino, 2,6 dimethylmorpholino, thiomorpholino, piperidyl, pyrrolidinyl, piperazinyl or N-methylpiperazinyl.

The group R₅ may be in position 3, 5 or 6 of the piperazine ring of compounds of formula (I)



When R represents halogen this is suitably chlorine or more preferably fluorine or when R is C₁₋₄ alkyl this is suitably methyl or ethyl wherein m is 0 or an integer from 1 to 2.

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Suitable values for R_1 or R_2 include hydrogen, a methyl, an ethyl or a propyl group.

5 R_1 and R_2 are suitably both hydrogen or suitably both a methyl group or suitably one of the R_1 and R_2 is a methyl group and the other is hydrogen.

Suitable values for R_3 include a methyl, an ethyl or a trifluoromethyl group.

10 When R_4 is $(CH_2)^q R_7$ or $(CH_2)^r CO(CH_2)^p R_7$, R_7 is suitably a hydrogen, hydroxy, furanyl, thiophenyl, imidazolyl, thiazolyl, oxazolyl, pyridyl, morpholino, piperidinyl, pyrrolidinyl, NR_9R_8 e.g. NH_2 , $NH(C_{1-4} \text{ alkyl})$ e.g. NH methyl or $N(C_{1-4} \text{ alkyl})_2$ e.g. $N(\text{methyl})_2$, $NH(C_{1-4} \text{ alkyl})NH_2$ e.g. $NH(\text{ethyl})NH_2$, $NH(C_{1-4} \text{ alkyl})\text{morpholino}$ or $NH(C_{1-4} \text{ alkyl})\text{pyridyl}$ wherein q is 1 or 2 and p or r are zero or an integer from 1 to 2.

15 Suitable values for R_5 include hydrogen, a C_{1-4} alkyl (e.g. methyl) group, $CONH_2$ or $CONHCH_3$.

20 R is preferably a halogen (e.g. fluorine) and /or a C_{1-4} alkyl (e.g. methyl) group and m is preferably zero or an integer from 1 to 2.

R_1 is preferably a hydrogen atom or a methyl group.

25 R_2 is preferably a hydrogen atom or a methyl group.

R_3 is preferably a trifluoromethyl group.

30 R_4 is preferably a hydrogen atom, an amino C_{1-4} alkyl (e.g. aminoethyl) group, aminoacetyl, amino(C_{1-4} alkyl)aminocarbonyl, morpholino(C_{1-4} alkyl aminocarbonyl), pyridyl C_{1-4} alkylamino carbonyl, piperidylcarbonyl.

35 R_5 is preferably a hydrogen atom or a methyl group.

A preferred class of compounds of formula (I) are those wherein R is a halogen (e.g. fluorine) and /or a C_{1-4} alkyl (e.g. methyl) group, wherein m

is 0,1 or 2. More preferably m is 2. Within this class those wherein R is at the 2 and 4 position are particularly preferred.

5 Compounds of formula (I) wherein R₃ is a trifluoromethyl group and n is 2 represent a preferred class of compounds and within this class R₃ is preferably at the 3 and 5 position.

10 Also a preferred class of compounds of formula (I) are those wherein R₁ or R₂ represent independently hydrogen or a methyl group, R₄ is hydrogen and R₅ is hydrogen or a methyl group.

15 A further preferred class of compounds of formula (I) are those wherein R₁ or R₂ represent independently hydrogen or a methyl group, R₄ is hydrogen and R₅ is hydrogen.

20 15 A further preferred class of compounds of formula (I) are those wherein R₄ is a (CH₂)_rCO(CH₂)_pR₇ group, wherein R₇ represents an amine group or a piperidinyl group or R₄ is a (CH₂)_qR₇ group wherein R₇ is an amine group. Within this class, those wherein p or r are zero or 1 or q is 1 or 2 are particularly preferred.

25 20 A particularly preferred group of compounds of formula (I) is that R is halogen and/or methyl, R₃ is trifluoromethyl at the 3 and 5 position, R₁ and R₂ are independently hydrogen or methyl, R₄ is hydrogen, an aminoacetyl piperidinecarbonyl or amino ethyl group and R₅ is hydrogen or a methyl group.

30 25 A further particularly preferred group of compounds of formula (I) is that R is halogen and/or methyl, R₃ is trifluoromethyl at the 3 and 5 position, R₁ and R₂ are independently hydrogen or methyl, R₄ is hydrogen and R₅ is hydrogen.

35 Suitable compounds according to the invention are:

2-(3-Isopropyl-phenyl)-piperazine-1-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide;

(+)-2-(4-fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide;

and pharmaceutically acceptable salts and solvates thereof.

Preferred compounds according to the invention are:

2-(4-fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide;

5 (-)-2-(4-fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide.

2-(2-Isopropyl-phenyl)-piperazine-1-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide;

10 2-(4-Fluoro-3-methyl-phenyl)-piperazine-1-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide;

2-(2,4-Difluoro-phenyl)-piperazine-1-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide;;

15 2-(4-fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid [1-(3,5-bis-trifluoromethyl-phenyl)ethyl]-methyl-amide;

(+)-2-(4-fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid [1-(3,5-bis-trifluoromethyl-phenyl)ethyl]-methyl-amide;

(-)-2-(4-fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid [1-(3,5-bis-trifluoromethyl-phenyl)ethyl]-methyl-amide;

2-(4-Fluoro-phenyl)- piperazine-1-carboxylic acid (3,4-bis-trifluoromethyl-benzyl)-methyl-amide;

20 2-Phenyl-piperazine-1-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl- amide;

2-(2,4-dichloro-phenyl)-piperazine-1-carboxylic acid (3,5-bistrifluoro methyl-benzyl)-methyl-amide;

25 2-(3,4-dichloro-phenyl)-piperazine-1-carboxylic acid (3,5-bistrifluoro methyl-benzyl)-methyl-amide;

2-(4-Fluoro-2-methyl-phenyl)-3-methyl-piperazine-1-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide;

30 2-(2-Methyl-4-Fluoro-phenyl)-6-Methyl- piperazine-1-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide;

and pharmaceutically acceptable salts and solvates thereof.

Particularly preferred compounds according to the invention are:

35

2-(4-fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid [1-(3,5-bis-trifluoromethyl-phenyl)ethyl]-methyl-amide; (mixture of enantiomers A/B);

2-(4-fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid [1-(3,5-bis-trifluoromethyl-phenyl)ethyl]-methyl-amide; (mixture of enantiomers C/D);
2-(4-fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid [1-(3,5-bis-trifluoromethyl-phenyl)ethyl]-methyl-amide; (enantiomer A);

5 2-(4-fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid [1-(3,5-bis-trifluoromethyl-phenyl)ethyl]-methyl-amide; (enantiomer C);
and pharmaceutically acceptable salts and solvates thereof;
2-(4-fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid [1-(3,5-bis-trifluoromethyl-phenyl)ethyl]-methyl-amide; acetate salt (enantiomer C);
10 4-(2-Amino-acetyl)-2-(4-fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide, and pharmaceutically acceptable salts and solvates thereof; 4-(2-Amino-acetyl)-2-(4-fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide, hydrochloride

15 The compounds of the invention are antagonists of tachykinins, including substance P and other neurokinins both in vitro and in vivo and are thus of use in the treatment of conditions mediated by tachykinins, including substance P and other neurokinins.

20 The compounds of the invention possess NK₁-receptor binding affinity as determined in vitro by their ability to displace [³H]- substance P (SP) from NK₁ receptors in cell membranes of U-373MG human astrocytoma cells. U-373MG membranes (25-35 μ g protein per tube) were prepared and
25 incubated with [³H]-SP (0.6-0.8nM) at 20°C for 40min. Non-specific binding was defined as that remaining in the presence of 1 μ M (+) CP-99,994.

30 NK₁-receptor binding affinity has been determined in vitro by the compounds' ability to displace [³H] - substance P (SP) from recombinant human NK₁ receptors expressed in Chinese Hamster Ovary (CHO) cell membranes.

35 CHO cell membranes were prepared by using a modification of the method described by Dam T and Quirion R (Peptides, 7:855-864, 1986). Thus ligand binding was performed in 0.4 ml of 50 mM HEPES, pH 7.4, containing 3 mM MnCl₂, 0.02% BSA, 0.5 nM [³H]Substance P (30-56 Ci/mmol, Amersham), a final membrane concentration of 25 μ g of

protein/ml, and the test compounds. The incubation proceeded at room temperature for 40 min. Non-specific binding was determined using excess of Substance P (1 μ M) and represents about 6% of the total binding.

5 Compounds of invention were further characterised in a functional assay for the determination of their inhibitory effect. Human-NK₁-CHO cells were stimulated with Substance P and the receptor activation was evaluated by measuring the accumulation of cytidinediphosphodiacylglycerol (CDP-DAG), which is the liponucleotide precursor of phosphatidylinositol diphosphate. CDP-DAG accumulates in

10 the presence of Li⁺ as a consequence of the receptor mediated activation of phospholipase C (PLC) (Godfrey, Biochem. J., 258:621-624, 1989). The method is described in detail by Ferraguti et al. (Mol. Cell. Neurosci., 5:269-276, 1994).

15 The action of the compounds of the invention at the NK₁ receptor may be determined by using conventional test. Thus the ability to bind at the NK₁ receptor was determined using the gerbil foot tapping model as described by Rupniak & Williams, Eur. Jur. of Pharmacol., 1994.

20 Compounds of the invention have also been found to exhibit anxiolytic activity in conventional tests. For example in marmoset human threat test (Costall et al., 1988).

25 Compounds of the invention may be useful in the treatment of CNS disorders in particular in the treatment or prevention of major depressive disorders including bipolar depression, unipolar depression, single or recurrent major depressive episodes with or without psychotic features, catatonic features, melancholic features, atypical features or postpartum onset, the treatment of anxiety and the treatment of panic disorders. Other mood disorders encompassed within the term major depressive disorders include dysthymic disorder with early or late onset and with or without atypical features, neurotic depression and social phobia; dementia of the Alzheimer's type, with early or late onset, with depressed mood; vascular dementia with depressed mood; mood disorders induced by alcohol, amphetamines, cocaine, hallucinogens, inhalants, opioids, phencyclidine, sedatives, hypnotics, anxiolytics and other substances;

schizoaffective disorder of the depressed type; and adjustment disorder with depressed mood. Major depressive disorders may also result from a general medical condition including, but not limited to, myocardial infarction, diabetes, miscarriage or abortion, etc.

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Compounds of the invention are useful as analgesics. In particular they are useful in the treatment of traumatic pain such as postoperative pain; traumatic avulsion pain such as brachial plexus; chronic pain such as arthritic pain such as occurring in osteo-, rheumatoid or psoriatic arthritis; 10 neuropathic pain such as post-herpetic neuralgia, trigeminal neuralgia, segmental or intercostal neuralgia, fibromyalgia, causalgia, peripheral neuropathy, diabetic neuropathy, chemotherapy-induced neuropathy, AIDS related neuropathy, occipital neuralgia, geniculate neuralgia, glossopharyngeal neuralgia, reflex sympathetic dystrophy, phantom limb 15 pain; various forms of headache such as migraine, acute or chronic tension headache, temporomandibular pain, maxillary sinus pain, cluster headache; odontalgia; cancer pain; pain of visceral origin; gastrointestinal pain; nerve entrapment pain; sport's injury pain; dysmenorrhoea; menstrual pain; meningitis; arachnoiditis; 20 musculoskeletal pain; low back pain e.g. spinal stenosis; prolapsed disc; sciatica; angina; ankylosing spondylitis; gout; burns; scar pain; itch; and thalamic pain such as post stroke thalamic pain.

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Compounds of the invention are also useful in the treatment of sleep disorders including dysomnia, insomnia, sleep apnea, narcolepsy, and circadian ritmic disorders.

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Compounds of the invention are also useful as anti-inflammatory agents. In particular they are useful in the treatment of inflammation in asthma, influenza, chronic bronchitis and rheumatoid arthritis; in the treatment of inflammatory diseases of the gastrointestinal tract such as Crohn's disease, ulcerative colitis, inflammatory bowel disease and non-steroidal anti-inflammatory drug induced damage; inflammatory diseases of the skin such as herpes and eczema; inflammatory diseases of the bladder 35 such as cystitis and urge incontinence; and eye and dental inflammation.

Compounds of the invention are also useful in the treatment of allergic disorders, in particular allergic disorders of the skin such as urticaria, and allergic disorders of the airways such as rhinitis.

- 5 Compounds of the invention are also useful in the treatment of emesis, i.e. nausea, retching and vomiting. Emesis includes acute emesis, delayed emesis and anticipatory emesis. The compounds of the invention are useful in the treatment of emesis however induced. For example, emesis may be induced by drugs such as cancer chemotherapeutic agents such as alkylating agents, e.g. cyclophosphamide, carmustine, lomustine and chlorambucil; cytotoxic antibiotics, e.g. dactinomycin, doxorubicin, mitomycin-C and bleomycin; anti-metabolites, e.g. cytarabine, methotrexate and 5- fluorouracil; vinca alkaloids, e.g. etoposide, vinblastine and vincristine; and others such as cisplatin, dacarbazine, procarbazine and hydroxyurea; and combinations thereof; radiation sickness; radiation therapy, e.g. irradiation of the thorax or abdomen, such as in the treatment of cancer; poisons; toxins such as toxins caused by metabolic disorders or by infection, e.g. gastritis, or released during bacterial or viral gastrointestinal infection; pregnancy; 10 vestibular disorders, such as motion sickness, vertigo, dizziness and Meniere's disease; post-operative sickness; gastrointestinal obstruction; reduced gastrointestinal motility; visceral pain, e.g. myocardial infarction or peritonitis; migraine; increased intracranial pressure; decreased intracranial pressure (e.g. altitude sickness); opioid analgesics, such as morphine; and gastro-oesophageal reflux disease, acid indigestion, over-indulgence of food or drink, acid stomach, sour stomach, waterbrash/regurgitation, heartburn, such as episodic heartburn, 15 nocturnal heartburn, and meal-induced heartburn and dyspepsia.
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Compounds of the invention are also useful in the treatment of gastrointestinal disorders such as irritable bowel syndrome; skin disorders such as psoriasis, pruritis and sunburn; vasospastic diseases such as angina, vascular headache and Reynaud's disease; cerebral ischaemia such as cerebral vasospasm following subarachnoid haemorrhage; fibrosing and collagen diseases such as scleroderma and eosinophilic fascioliasis; disorders related to immun enhancement or

suppression such as systemic lupus erythematosus and rheumatic diseases such as fibrositis; and cough.

5 The compounds of the invention are of particular use in the treatment of depressive states, in the treatment of anxiety and of panic disorders. Depressive states include major depressive disorders including bipolar depression, unipolar depression, single or recurrent major depressive episodes with or without psychotic features, catatonic features, melancholic features, atypical features or postpartum onset, dysthymic 10 disorder with early or late onset and with or without atypical features, neurotic depression and social phobia; dementia of the Alzheimer's type, with early or late onset, with depressed mood; vascular dementia with depressed mood; mood disorders induced by alcohol, amphetamines, cocaine, hallucinogens, inhalants, opioids, phencyclidine, sedatives, 15 hypnotics, anxiolytics and other substances; schizoaffective disorder of the depressed type.

20 The invention therefore provides a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof for use in therapy, in particular in human medicine.

25 There is also provided as a further aspect of the invention the use of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof in the preparation of a medicament for use in the treatment of conditions mediated by tachykinins, including substance P and other neurokinins.

30 In an alternative or further aspect there is provided a method for the treatment of a mammal, including man, in particular in the treatment of conditions mediated by tachykinins, including substance P and other neurokinins, comprising administration of an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

35 It will be appreciated that reference to treatment is intended to include prophylaxis as well as the alleviation of established symptoms. Compounds of formula (I) may be administered as the raw chemical but

the active ingredient is preferably presented as a pharmaceutical formulation.

5 Accordingly, the invention also provides a pharmaceutical composition which comprises at least one compound of formula (I) or a pharmaceutically acceptable salt thereof and formulated for administration by any convenient route. Such compositions are preferably in a form adapted for use in medicine, in particular human medicine, and can conveniently be formulated in a conventional manner using one or
10 more pharmaceutically acceptable carriers or excipients.

15 Thus compounds of formula (I) may be formulated for oral, buccal, parenteral, topical (including ophthalmic and nasal), depot or rectal administration or in a form suitable for administration by inhalation or insufflation (either through the mouth or nose).

20 For oral administration, the pharmaceutical compositions may take the form of, for example, tablets or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g. pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g. lactose, microcrystalline cellulose or calcium hydrogen phosphate); lubricants (e.g. magnesium stearate, talc or silica); disintegrants (e.g. potato starch or sodium starch glycollate); or wetting agents (e.g. sodium lauryl sulphate). The tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable
25 additives such as suspending agents (e.g. sorbitol syrup, cellulose derivatives or hydrogenated edible fats); emulsifying agents (e.g. lecithin or acacia); non-aqueous vehicles (e.g. almond oil, oily esters, ethyl alcohol or fractionated vegetable oils); and preservatives (e.g. methyl or propyl-p-hydroxybenzoates or sorbic acid). The preparations may also contain buffer salts, flavouring, colouring and sweetening agents as appropriate.

Preparations for oral administration may be suitably formulated to give controlled release of the active compound.

5 For buccal administration the composition may take the form of tablets or lozenges formulated in conventional manner.

10 The compounds of the invention may be formulated for parenteral administration by bolus injection or continuous infusion. Formulations for injection may be presented in unit dosage form e.g. in ampoules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising and/or dispersing agents. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile pyrogen-free water, before use.

15 The compounds of the invention may be formulated for topical administration in the form of ointments, creams, gels, lotions, pessaries, aerosols or drops (e.g. eye, ear or nose drops). Ointments and creams may, for example, be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling agents. Ointments for administration to the eye may be manufactured in a sterile manner using sterilised components.

20 25 Lotions may be formulated with an aqueous or oily base and will in general also contain one or more emulsifying agents, stabilising agents, dispersing agents, suspending agents, thickening agents, or colouring agents. Drops may be formulated with an aqueous or non-aqueous base also comprising one or more dispersing agents, stabilising agents, solubilising agents or suspending agents. They may also contain a preservative.

30 35 The compounds of the invention may also be formulated in rectal compositions such as suppositories or retention enemas, e.g. containing conventional suppository bases such as cocoa butter or other glycerides.

The compounds of the invention may also be formulated as depot preparations. Such long acting formulations may be administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds of the

5 invention may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

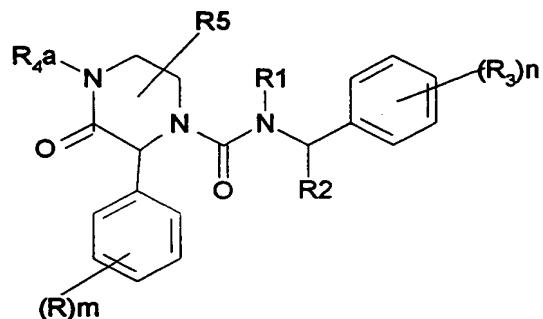
10 For intranasal administration, the compounds of the invention may be formulated as solutions for administration via a suitable metered or unitary dose device or alternatively as a powder mix with a suitable carrier for administration using a suitable delivery device.

15 A proposed dose of the compounds of the invention is 1 to about 1000mg per day. It will be appreciated that it may be necessary to make routine variations to the dosage, depending on the age and condition of the patient and the precise dosage will be ultimately at the discretion of the attendant physician or veterinarian. The dosage will also depend on the

20 route of administration and the particular compound selected.

Compounds of formula (I), and salts and solvates thereof, may be prepared by the general methods outlined hereinafter. In the following description, the groups R, R₁, R₂, R₄, R₅, m, n, p, q and r have the meaning as previously defined for compounds of formula (I) unless otherwise stated.

According to general process (A), a compound of formula (I) wherein R₄ is hydrogen or a (CH₂)_qR₇ group as defined in formula (I), provided that when R₅ is a C₁₋₄ alkyl or a COR₆ group, R₅ is not in 3 position of the piperazine ring, may be prepared by reduction of a ketopiperazine of formula (II), wherein R_{4a} is hydrogen or a suitable nitrogen protecting group or R_{4a} is a (CH₂)_qR₇ group or protecting derivatives thereof followed where necessary or desired by removal of any protecting group.



(II)

5

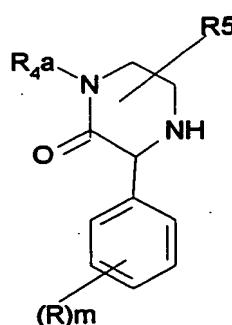
The reaction may be carried out using a suitable metal reducing agent such as a metal hydride, for example a borane hydride, alane hydride or a metal hydride complex like lithium aluminum hydride or sodium borohydride, or an organo-metallic complex such as borane- methyl sulphide, 9-borabicyclononane (9-BBN), triethylsilane, sodium triacetoxyborohydride, sodium cyanoborohydride.

Suitable solvents for this reaction are ether (e.g tetrahydrofuran), or halohydrocarbon (e.g. dichloromethane) or an amide (e.g. N,N-dimethylformamide) at a temperature within the range of room

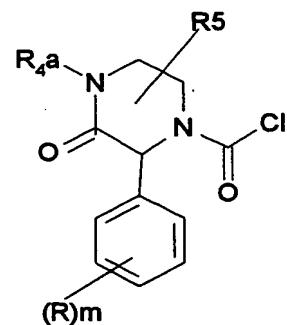
15 temperature to the reflux temperature of the reaction mixture.

Compounds of formula (II) may be prepared by treating compounds of formula (III) wherein R_{4a} and R₅ have the meaning defined in formula (II)

20



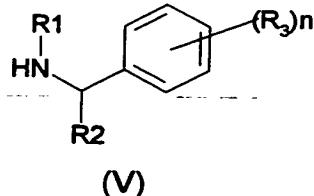
(III)



(IV)

with triphosgene in aprotic solvent such as dichloromethane and in the presence of an organic base such triethylamine to form the intermediate carbonyl chloride compound (IV) which may be isolated if required, followed by reaction of compound (IV) with the amine compound (V)

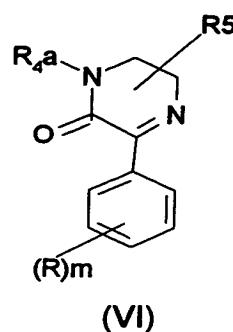
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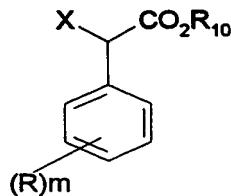
10 The reaction conveniently takes place in an aprotic solvent such as a hydrocarbon, a halohydrocarbon such as dichloromethane or an ether such as tetrahydrofuran optionally in the presence of a base such as a tertiary amine e.g. diisopropyl ethyl amine.

15 Compounds of formula (III) are either known compounds or may be prepared by analogous method. Thus for example a compound of formula (III) may be prepared by reduction of a dihydropyrazin-2-one (VI) using a suitable metal reducing agent such as sodium borohydride. Alternatively, catalytic hydrogenation may be used, for example using Palladium on Carbon catalyst in a suitable solvent such as methanol.

20

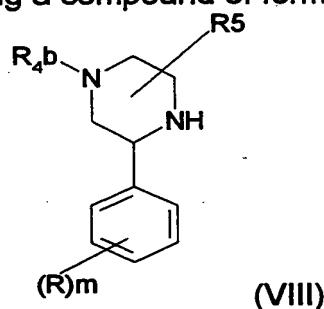


25 Alternatively compounds of formula (III) wherein R₅ is hydrogen may be prepared by reaction of compounds of formula (VII), wherein R₁₀ is a C₁₋₄ alkyl group and X is a suitable leaving group such as halogen, i.e. bromine or iodine atom, or OSO₂CF₃,

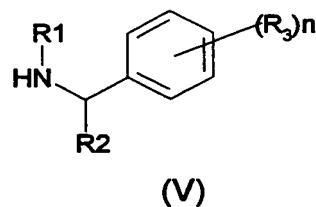


5 with ethylenediamine. The reaction conveniently takes place in a suitable solvent such as alcohol (i.e. ethanol) at an elevated temperature.

10 According to a further general process (B) a compound of formula (I) wherein R₄ is hydrogen or (CH₂)_rCO(CH₂)_pR₇ as above defined may be prepared by reacting a compound of formula (VIII),



15 wherein R_{4b} represents a nitrogen protecting group or R_{4b} is (CH₂)_rCO(CH₂)_pR₇ or a protecting group thereof, with triphosgene in an aprotic solvent such as dichloromethane and in the presence of an organic base such triethylamine to form the intermediate carbonyl chloride compound (IV) which may be isolated if required, followed by reaction of compound (IV) with the amine compound (V)



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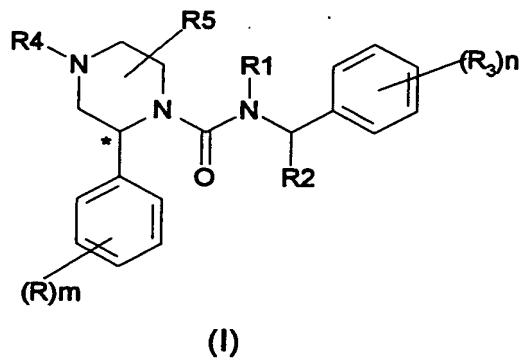
The reaction conveniently takes place in an aprotic solvent such as a hydrocarbon, a halohydrocarbon such as dichloromethane or an ether

such as tetrahydrofuran optionally in the presence of a base such as a tertiary amine e.g. diisopropyl ethyl amine, followed by deprotection where necessary.

5 When R_{4a} or R_{4b} is nitrogen protecting group examples of suitable groups include alkoxy carbonyl e.g. t-butoxycarbonyl, benzyloxycarbonyl, arylsulphonyl e.g. phenylsulphonyl or 2-trimethylsilyl ethoxymethyl.

10 Protection and deprotection may be effected using conventional techniques such as those described in "Protective Groups in Organic Synthesis 2nd Ed." by T.W. Greene and P. G. M. Wuts (John Wiley and Sons, 1991) and as described in the examples hereinafter.

15 Compounds of formula (I) wherein R₄ is a CO(CH₂)_pR₇ group or protective derivatives thereof may be also prepared by reaction of the compound of formula (I)



20 wherein R₄ is a hydrogen atom, with an activated derivative of the acid R₇(CH₂)_pCO₂H(IX).

25 The activated derivatives of the carboxylic acid (IX) may be prepared by conventional means. Suitable activated derivatives of the carboxylic group include the corresponding acyl halide, mixed anhydride, activated ester such as thioester or the derivative formed between the carboxylic acid group and a coupling agent such as that used in peptide chemistry, for example carbonyl diimidazole or a diimide such as 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide

30 The reaction is preferably carried out in an aprotic solvent such as an amide e.g. N,N-dimethylformamide or acetonitrile.

Compounds of formula (I) wherein R_4 is $CONR_9R_8$ in which R_9 or R_8 have the meaning defined in formula (I) may be prepared by reaction of a compound of formula (I) wherein R_4 is a hydrogen atom with triphosgene in an aprotic solvent such as dichloromethane and in the presence of an organic base such as triethylamine followed by reaction with the amine compound $NR_9R_8(X)$.

Alternatively compounds of formula (I) wherein R_4 is a $CONHR_9$ group in which R_9 is C_{1-4} alkyl may be also prepared by reaction with isocyanate of formula $R_9NC=O$ (XI). The reaction with the compound (XI) is conveniently carried out in a solvent such as tetrahydrofuran or aqueous tetrahydrofuran, a halohydrocarbon (e.g. dichloromethane) or acetonitrile optionally in the presence of a base such as triethylamine and at temperature within the range 0-80°C.

In a further embodiment compounds of formula (I) wherein R_4 is $(CH_2)qR_7$ or R_4 is $(CH_2)rCO(CH_2)pR_7$ wherein q , r and R_7 have the meanings defined in formula (I) or are protective derivatives thereof with the provision that r is not zero, may also be prepared by reaction of compounds of formula (I) wherein R_4 is a hydrogen group with a compound of formula (XII) $R_7(CH_2)qX$ or $X(CH_2)rCO(CH_2)pR_7$ (XIII), in which X is a leaving group such as halogen e.g. chlorine, a bromine atom, a mesyl or a tosyl group.

In a further preferred embodiment compounds of formula (I) wherein R_4 is $(CH_2)qR_7$ wherein q and R_7 have the meanings defined in formula (I) or are protective derivatives thereof may be also prepared by reaction of compounds of formula (I) wherein R_4 is a hydrogen group with a compound of formula (XIV) $R_7(CH_2)qCHO$ (XIV), in which q is zero or an integer from 1 to 3 and R_7 has the meanings defined in formula (I) or are protective derivatives thereof, in the presence of suitable metal reducting agent such as $NaCNBH_3$.

Where it is desired to isolate a compound formula (I) as a salt, for example a pharmaceutically acceptable salt, this may be achieved by reacting the compound of formula (I) in the form of the free base with an appropriate amount of suitable acid and in a suitable solvent such as an

alcohol (e.g. ethanol or methanol), an ester (e.g. ethyl acetate) or an ether (e.g. diethyl ether or tetrahydrofuran).

5 Compounds of formula (VI) and (VIII) are known compounds or may be prepared by analogous methods to those used for known compounds.

10 Pharmaceutically acceptable salts may also be prepared from other salts, including other pharmaceutically acceptable salts, of the compound of formula (I) using conventional methods.

15 The compounds of formula (I) may readily be isolated in association with solvent molecules by crystallisation from or evaporation of an appropriate solvent to give the corresponding solvates.

20 When a specific enantiomer of a compound of general formula (I) is required, this may be obtained for example by resolution of a corresponding enantiomeric mixture of a compound of formula (I) using conventional methods.

25 Thus specific enantiomers of the compounds of formula (I) in which R₄ is an hydrogen atom may be prepared by reaction of a suitable chiral alcohol, in the presence of a source of a carbonyl group (such as triphosgene or carbonyl diimidazole) separating the resultant diastereoisomeric carbamates by conventional means e.g. chromatography or by fractional crystallisation. The required enantiomer of a compound of general formula (I) may be isolated by removal of carbamate and conversion into the required free base or salts thereof.

30 Suitable chiral alcohol for use in the process include (R)-sec-phenylethyl alcohol, etc.

35 Alternatively, enantiomers of a compound of general formula (I) may be synthesised from the appropriate optically active intermediates using any of the general processes described herein.

Thus for example the required enantiomer may be prepared by the corresponding enantiomeric amine of formula (III) using any of the processes described above for preparing compounds of formula (I) from the amine (III). The enantiomer of amine (III) may be prepared from the

racemic amine (III) using conventional procedures such as salt formation with a suitable optically active acid such as L(+)mandelic acid.

The invention is further illustrated by the following Intermediates and Examples which are not intended as a limitation of the invention.

In the Intermediates and Examples unless otherwise stated:

Melting points (m.p.) were determined on a Gallenkamp m.p. apparatus

and are uncorrected. All temperatures refers to °C. Infrared spectra were measured on a FT-IR instrument. Proton Magnetic Resonance (¹H-NMR) spectra were recorded at 400 MHz, chemical shifts are reported in ppm downfield (d) from Me₄Si, used as internal standard, and are assigned as singlets (s), doublets (d), doublets of doublets (dd), triplets (t), quartets (q) or multiplets (m). Column chromatography was carried out over silica gel (Merck AG Darmstaadt, Germany). The following abbreviations are used in text: EA = ethyl acetate, CH = cyclohexane, DCM = dichloromethane, THF = tetrahydrofuran, TFA = trifluoroacetic acid, TEA = triethylamine, PPA = polyphosphoric acid, DBU = 1,8-diazobicyclo [5,4,0]undec-7-ene, DMSO = dimethylsulphoxide, IMS=mixture of Ethanol with 5% of methanol, LHDMs=Lithiumbis(trimethylsilyl)amide DIPEA=diisopropylethylamine Tlc refers to thin layer chromatography on silica plates, and dried refers to a solution dried over anhydrous sodium sulphate; r.t. (RT) refers to room temperature.

Enantiomer A or enantiomer B refer to a single enantiomer whose absolute stereochemistry was not characterised.

Intermediate 1

2-Methyl-4-fluoroboronic acid

To magnesium turnings (0.5g), heated at 90°C, a solution of commercial 2-bromo-5-fluorotoluene (2ml) in THF (3ml) was added drop-wise. The reaction mixture was heated at 90-95°C for 1 ½ hr, and then the mixture was diluted with other THF (10ml) and transferred in a dropping funnel.

The latter solution and trimethylborate (2.1ml) were simultaneously added to stirred diethyl ether (15ml), maintaining the temperature below -60°C. The reaction mixture was allowed to warm to r.t., then the stirring

was continued for 1 1/2 hr. Water (6ml) was added and the reaction mixture was stirred overnight. Ethyl acetate was added and the solution was washed with 1N HCl and brine. The organic phase was next dried with Na_2SO_4 and concentrated to give the crude product which was 5 triturated in diethyl ether/petroleum (25ml/75ml) to obtain the title compound as a trimer (1.44g, white powder).

NMR (DMSO) δ (ppm) 7.87 (m, 3H), 6.99-6.93 (m, 6H), 2.6 (s, 9H)

Intermediate 2

10 **2-(4-fluoro-2-methyl-phenyl)-pyrazine.**

A mixture of intermediate 1 (1.34g), 2-chloropyrazine (1ml) and bis[1,2-bis(diphenylphosphino)ethane]-palladium(0) (0.21g) in toluene/1M sol. Na_2CO_3 /EtOH95% 20ml/20ml/10ml was heated at reflux for 2 hr. The 15 solution was poured into ethyl acetate and washed with brine. The organic phase was next dried with Na_2SO_4 and concentrated to give the crude product, which was purified by flash column chromatography to obtain the title compound (1.4g) as a white powder.

m.p.=66-68°C

20 NMR (DMSO) δ (ppm) 8.81 (d, 1H), 8.72 (m, 1H), 8.63 (d, 1H), 7.52 (m, 1H), 7.22 (m, 1H), 7.17 (m, 1H), 2.35 (s, 3H).

Intermediate 3

2-(3-Isopropyl-phenyl)-pyrazine

To a solution of commercial 3-isopropyl-benzene boronic acid (1.0g) in a 2:2:1 mixture of toluene/1M Na_2CO_3 /EtOH (122 mL), at r.t., 25 2-chloropyrazine (599 μL) and the bis[1,2-bis(diphenylphosphino)ethane]-palladium(0) catalyst (110mg) were added. The reaction mixture was heated at 80°C for 3 hr. It was then cooled down and partitioned between EtOAc/sat.aq. NaCl. The phases were separated and the organic layer 30 was dried over Na_2SO_4 . The solids were filtered and the solvent evaporated. The crude oil was purified by flash chromatography obtaining the title compound as a clear oil (468 mg).

NMR (CDCl_3): δ (ppm) 9.02 (d, 1H), 8.63 (m, 1H), 8.49 (d, 1H), 7.89 (m, 1H), 7.80 (m, 1H), 7.44 (t, 1H), 7.35 (d, 1H), 3.02 (m, 1H), 1.31 (d, 6H).

Intermediate 4**2-(2-Isopropyl-phenyl)-pyrazine**

1) To a suspension of magnesium turnings (134 mg) in anh. THF (2.5 mL), at r.t., under N₂, a small crystal of I₂ was added, followed by 10% of a solution of commercial 1-bromo-2-isopropyl-benzene (1.0 g) in anh. THF (2.6 mL). The suspension was heated gently (heat gun) until the brown colour disappeared. The rest of the bromide solution was added drop-wise, maintaining the reaction mixture warm (50-60°C) with an oil bath. After the addition was complete (15 min) the suspension was stirred at 60°C until the magnesium turnings had almost completely reacted (2 hr). The new brown solution was used in the next step.

5 2) To a solution of the 2-chloropyrazine (448 µL) in anh. THF (5.1 mL), at 0°C, under N₂, [1,2-bis(diphenylphosphino)ethane]dichloronickel(II) (100mg) and the Grignard solution were successively added drop-wise.

10 15 The brown solution was stirred at r.t. for 30 min, then at reflux for 3 hr. It was then poured in sat.aq. NaCl/CH₂Cl₂ and the phases were separated. The aqueous layer was extracted with CH₂Cl₂ (2x) and the combined organic extracts were dried over Na₂SO₄. The solids were filtered and the solvent evaporated. The crude oil obtained was purified by flash chromatography obtaining the title compound as a yellow oil (676 mg).

20 NMR (CDCl₃): δ (ppm) 8.67 (d, 1H), 8.67 (m, 1H), 8.54 (d, 1H), 7.5-7.3 (m, 4H), 3.13 (m, 1H), 1.20 (d, 6H).

Intermediate 5

25 2) To a solution of the 2-chloropyrazine (472 µL) in anh. THF (5.3 mL), at 0°C, under N₂, [1,2-bis(diphenylphosphino)ethane]dichloronickel(II) (100mg) and the Grignard solution were successively added drop-wise.

1) To a suspension of magnesium turnings (167 mg) in anh. THF (2.6 mL), at r.t., under N₂, a small crystal of I₂ was added, followed by 10% of a solution of commercial 4-bromo-1-fluoro-2-methyl-benzene (1.0g) in anh. THF (2.7 mL). The suspension was heated gently (heat gun) until the brown colour disappeared. The rest of the bromide solution was added drop-wise, maintaining the reaction mixture warm (50-60°C) with an oil bath. After the addition was complete (15 min) the suspension was stirred at 60°C until the magnesium turnings had almost completely reacted (2 hr). The new brown solution was used in the next step.

30 35

The brown solution was stirred at r.t. for 30 min, then at reflux for 3 hr. It was then poured in sat.aq. NaCl/CH₂Cl₂ and the phases were separated. The aqueous layer was extracted with CH₂Cl₂ (2x) and the combined organic extracts were dried over Na₂SO₄. The solids were filtered and the solvent evaporated. The crude oil obtained was purified by flash chromatography. The title compound was obtained as a yellow oil (571mg).

NMR-(CDCl₃): δ-(ppm)- 8.98 (d, 1H), 8.60 (m, 1H), 8.49 (d, 1H), 7.87 (m, 1H), 7.80 (m, 1H), 7.13 (t, 1H), 2.37 (s, 3H).

10

Intermediate 6

2-(2,4-Difluoro-phenyl)-pyrazine

1) To a suspension of magnesium turnings (139 mg) in anh. THF (2.6 mL), at r.t., under N₂, a small crystal of I₂ was added, followed by 10% of a solution of commercial 1-bromo-2,4-difluoro-benzene (1.0 g) in anh. THF (2.6 mL). The suspension was heated gently (heat gun) until the brown-colour-disappeared. The rest of the bromide solution was added drop-wise, maintaining the reaction mixture warm (50-60°C) with an oil bath. After the addition was complete (15 min) the suspension was stirred at 60°C until the magnesium turnings had almost completely reacted (2 hr). The new brown solution was used in the next step.

2) To a solution of the 2-chloropyrazine (463 μL) in anh. THF (5.2 mL), at 0°C, under N₂, [1,2-bis(diphenylphosphino)ethane]dichloronickel(II) (50mg) and the Grignard solution were successively added drop-wise.

25 The brown solution was stirred at r.t. for 30 min, then at reflux for 3 hr. It was then poured in sat.aq. NaCl/CH₂Cl₂ and the phases were separated. The aqueous layer was extracted with CH₂Cl₂ (2x) and the combined organic extracts were dried over Na₂SO₄. The solids were filtered and the solvent evaporated. The crude oil obtained was purified by flash chromatography. The title compound was obtained as a yellow solid (175mg).

30 NMR (CDCl₃): δ (ppm) 9.01 (dd, 1H), 8.78 (dd, 1H), 8.66 (d, 1H), 7.99 (td, 1H), 7.47 (td, 1H), 7.29 (td, 1H).

35

Intermediate 7

2-(4-fluoro-2-methyl-phenyl)-piperazine hydrochloride.

A two neck round bottom flask was equipped with a water condenser and a dropping funnel and was flushed with N_2 . Mg turnings (1.45g) were introduced in the flask and were suspended in anh. THF (5 mL). A small crystal of I_2 was added in order to activate the Mg. The dropping funnel was filled with a solution of the commercial 2-bromo-5-fluorotoluene (10g) in anh. THF (30 mL). The solution of the bromide was added drop-wise to the Mg turnings and the solution warmed up to approximately 70°C. The solution was kept at that temperature until the complete disappearance of the Mg turnings.

5 Meanwhile, 2-chloropyrazine (4.75 mL) was dissolved in anh. THF (30 mL) and [1,2-bis(diphenylphosphino)ethane]dichloronickel(II) (510mg) was added. To this suspension the solution of Grignard was added drop-wise, at 0°C, under N_2 . After the addition was complete, the reaction mixture was heated at reflux for 2 hr. The THF was evaporated, the residue poured in sat. aq. NaCl and the aqueous phase was extracted with CH_2Cl_2 (3x). The organic extracts were dried over Na_2SO_4 , the solids were filtered and the solvent evaporated. The crude oil was purified by flash chromatography and then through a small column of Florisil (eluant: CH_2Cl_2) to eliminate the nickel residue (6.0 g). 2-(4-fluoro-2-methyl-phenyl)-pyrazine (6.0 g) was obtained as a pale yellow solid.

10 2-(4-fluoro-2-methyl-phenyl)-pyrazine (0.3g) dissolved in EtOH 95% (20ml) and 37% HCl (0.2ml) was hydrogenated at 5 atm. for 4hr, in the presence of 20% $Pd(OH)_2/C$ (30mg) as catalyst. The catalyst was filtered off and the solvent was evaporated. The crude residue was triturated in MeOH/AcOEt (5ml/15ml) to obtain the title compound (0.08g) as a white powder.

15 m.p. >220 °C

20 NMR (DMSO) δ (ppm) 9.72 (broad, 2H), 7.90 (d, 1H), 7.21-7.17 (m, 2H), 4.85 (m, 1H), 3.57-3.2 (m, 6H), 2.40 (s, 3H).

Intermediate 8

3-(4-fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid benzyl ester

25 To a solution of intermediate 7 (0.25g) and triethylamine (0.5ml) in CH_2Cl_2 (15ml) a solution of benzylchloroformate (0.15ml) in CH_2Cl_2

(10ml) was added drop-wise, at 0°C. The reaction mixture was stirred at 0°C for 2hr, then washed with brine. The organic phase was next dried with Na_2SO_4 and concentrated to give the crude product, which was purified by flash column chromatography to obtain the title compound (0.21g) as a colourless oil.

5 $\text{NMR} (\text{CDCl}_3, 40^\circ\text{C}) \delta$ (ppm) 7.52 (m, 1H), 7.4-7.3 (m, 5H), 6.9-6.8 (m, 2H), 5.16 (dd, 2H), 4.12 (m, 2H), 3.86 (m, 1H), 3.3-2.7 (m, 4H), 2.33, (bs, 3H).

10 **Intermediate 9**

3-(3-Isopropyl-phenyl)-piperazine-1-carboxylic acid benzyl ester

To a solution of intermediate 3 (428 mg) in anh. EtOH (47 mL), at r.t., under N_2 , conc. HCl (492 μL) and $\text{Pd}(\text{OH})_2/\text{C}$ 20% (86 mg, 20% wt) were added. The black suspension was placed in a PARR apparatus and the 15 hydrogenation was done at r.t. under 7 atm of H_2 for 18 hr. The catalyst was then filtered on Celite and the Celite cake rinsed with MeOH. The filtrate was evaporated to dryness. The grey solid 2-(3-Isopropyl-phenyl)-piperazine hydrochloride (654 mg) was dissolved in anh. CH_2Cl_2 (24 mL), at 0°C, under N_2 , then triethylamine (1.32 mL) and 20 benzylchloroformate (404 μL) were added. The solution was stirred at 0°C for 2 $\frac{1}{2}$ hr. It was then poured in CH_2Cl_2 /sat.aq. NaCl /sat.aq. K_2CO_3 and the phases were separated. The aqueous layer was extracted with CH_2Cl_2 (1x) and the combined organic extracts were dried over Na_2SO_4 . The solids were filtered and the solvent evaporated. The 25 crude oil was purified by flash chromatography. The title compound was obtained as a yellow oil (192mg).

$\text{NMR} (\text{CDCl}_3)$: δ (ppm) 7.34-7.12 (m, 8H), 5.08 (m, 2H), 3.89 (bd, 1H), 3.85 (bm, 1H), 3.55 (bd, 1H), 3.0-2.65 (bm, 6H), 1.17 (d, 6H).

30 **Intermediate 10**

3-(2-Isopropyl-phenyl)-piperazine-1-carboxylic acid benzyl ester.

To a solution of intermediate 4 (315mg) in anh. EtOH (40 mL), at r.t., under N_2 , conc. HCl (529 μL) and $\text{Pd}(\text{OH})_2/\text{C}$ 20% (63mg, 20% wt) were added. The black suspension was placed in a PARR apparatus and the 35 hydrogenation was done at r.t. und r 7 atm of H_2 for 18 hr. The catalyst was then filtered on Celite and the Celite cake rinsed with MeOH. Th filtrate was vaporated to dryness. The grey solid 2-(2-Isopropyl-phenyl)-

piperazine hydrochloride (411mg) was dissolved in anh. CH_2Cl_2 (16 mL), at 0°C, under N_2 , then triethylamine (886 μL) and benzylchloroformate (272 μL) were added. The solution was stirred at 0°C for 2.5 hr. It was then poured in CH_2Cl_2 /sat.aq. NaCl/sat.aq. K_2CO_3 and the phases were separated. The aqueous layer was extracted with CH_2Cl_2 (1x) and the combined organic extracts were dried over Na_2SO_4 . The solids were filtered and the solvent evaporated. The crude oil was purified by flash chromatography obtaining the title compound as a yellow oil (117mg).

NMR (CDCl_3): δ (ppm) 7.52 (d, 1H), 7.4-7.3 (m, 5H), 7.26 (d, 1H), 7.21 (t, 1H), 7.14 (t, 1H), 5.14 (d, 1H), 5.03 (d, 1H), 4.0-3.8 (m, 3H), 3.23 (m, 1H), 2.99 (m, 1H), 2.91 (m, 1H), 2.8-2.0 (m, 2H), 1.19 (d, 6H).

Intermediate 11

3-(4-Fluoro-3-methyl-phenyl)-piperazine-1-carboxylic acid benzyl ester

To a solution of intermediate 5 (314mg) in anh. EtOH (30 mL), at r.t., under N_2 , conc. HCl (350 μL) and $\text{Pd}(\text{OH})_2/\text{C}$ 20% (30mg, 10% wt) were added. The black suspension was placed in a PARR apparatus and the hydrogenation was done at r.t. under 7 atm of H_2 for 18 hr. The catalyst was then filtered on Celite and the Celite cake rinsed with MeOH. The filtrate was evaporated to dryness. The grey solid 2-(4-Fluoro-3-methyl-phenyl)-piperazine hydrochloride (411mg) was dissolved in anh. CH_2Cl_2 (15 mL), at 0°C, under N_2 , then triethylamine (858 μL) and benzylchloroformate (264 μL) were added. The solution was stirred at 0°C for 2.5 hr. It was then poured in CH_2Cl_2 /sat.aq. NaCl/sat.aq. K_2CO_3 and the phases were separated. The aqueous layer was extracted with CH_2Cl_2 (1x) and the combined organic extracts were dried over Na_2SO_4 . The solids were filtered and the solvent evaporated. The crude oil was purified by flash chromatography obtaining the title compound as a yellow oil (170mg).

NMR (CDCl_3): δ (ppm) 7.3-7.4 (m, 5H), 7.23 (m, 1H), 7.17 (m, 1H), 6.96 (t, 1H), 5.17 (m, 2H), 4.15 (m, 2H), 3.67 (m, 1H), 2.7-3.2 (m, 4H), 2.27 (s, 3H).

Intermediate 12

3-(2,4-Difluoro-phenyl)-piperazine-1-carboxylic acid benzyl ester

To a solution of intermediate 6 (175mg) in anh. EtOH (30 mL), at r.t., under N₂, conc. HCl (228 μ L, 2.5 eq) and Pd(OH)₂/C 20% (20mg, 10% wt) were added. The black suspension was placed in a PARR apparatus and the hydrogenation was done at r.t. under 7 atm of H₂ for 18 hr. The catalyst was then filtered on Celite and the Celite cake rinsed with MeOH. The filtrate was evaporated to dryness. The greenish solid 2-(2,4-Difluoro-phenyl)-piperazine hydrochloride (247mg) was dissolved in anh. CH₂Cl₂ (9.1 mL), at 0°C, under N₂, then triethylamine (508 μ L) and benzylchloroformate (162 μ L) were added. The solution was stirred at 10 0°C for 3 hr. It was then poured in CH₂Cl₂/sat.aq. NaCl/sat.aq. K₂CO₃ and the phases were separated. The aqueous layer was extracted with CH₂Cl₂ (1x) and the combined organic extracts were dried over Na₂SO₄. The solids were filtered and the solvent evaporated. The crude oil was purified by flash chromatography obtaining the title compound as a 15 yellow oil (100mg).

NMR (CDCl₃): δ (ppm) 7.49 (m, 1H), 7.3-7.4 (m, 5H), 6.76-6.8 (m, 2H), 5.16 (s, 2H), 4.15 (m, 2H), 4.03 (m, 1H), 2.8-3.15 (m, 4H).

Intermediate 13

20 **4-[(3,5-bis-trifluoromethyl-benzyl)-methyl-carbamoyl]-3-(4-fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid benzyl ester.**
To a solution of intermediate 8 (0.05g) and triethylamine (0.15ml) in CH₂Cl₂ (10ml), a solution of triphosgene (0.02ml) in CH₂Cl₂ (10ml) was added drop-wise, at 0°C. The reaction mixture was allowed to warm to r.t. 25 in 3hr, then diisopropylethylamine (0.07ml) and (3,5-bis-trifluoromethyl-benzyl)-methyl-amine hydrochloride (53mg) were added. The reaction mixture was stirred at reflux for 2hr and at r.t. overnight, then was washed with a 1N solution of HCl and brine. The organic phase was next dried with Na₂SO₄ and concentrated to give the crude product, which was 30 purified by flash column chromatography to obtain the title compound (0.05g) as a colourless oil.
NMR (CDCl₃): δ (ppm) 7.76 (s, 1H), 7.49 (s, 2H), 7.4-7.3 (m, 5H), 7.20 (dd, 1H), 6.86 (d, 1H), 6.79 (m, 1H), 5.17 (s, 2H), 4.66 (d, 1H), 4.64 (m, 1H), 4.36 (d, 1H), 3.97 (m, 2H), 3.4 (m, 2H), 3.16 (m, 2H), 2.93 (s, 3H), 35 2.38 (bs, 3H).

Intermediate 144-[(3,5-Bis-trifluoromethyl-benzyl)-methyl-carbamoyl]-3-(3-isopropyl-phenyl)piperazine-1-carboxylic acid benzyl ester

To a solution of intermediate 9 (192 mg) in anh. CH_2Cl_2 (7 mL), at 0°C, under N_2 , triethylamine (237 μL) was added. To this solution a solution of triphosgene (76mg) in anh. CH_2Cl_2 (4 mL) was added drop-wise. The reaction was stirred at 0°C for 2 hr.

To this solution diisopropylethylamine (198 μL) and (3,5-bis-trifluoromethyl-benzyl)-methyl-amine hydrochloride (200 mg) were added.

The solution was stirred at r.t. for 18 hr. The reaction mixture was diluted with CH_2Cl_2 , washed with 10% citric acid (1x) and dried over Na_2SO_4 . The solids were filtered and the solvent evaporated. The crude oil was purified by flash chromatography. The title compound was obtained as a thick oil (353 mg).

NMR (CDCl_3): δ (ppm) 7.91 (bs, 1H), 7.84 (bs 2H), 7.36-7.26 (m, 5H), 7.18-7.10 (m, 2H), 7.06 (m, 2H), 5.07 (s, 2H), 4.76 (t, 1H), 4.50 (bs, 2H), 3.96 (dd, 1H), 3.66 (td, 1H), 3.57 (dd, 1H), 3.4-3.3 (m, 2H), 3.19 (m, 1H), 2.86 (s, 3H), 2.76 (m, 1H), 1.09 (2d, 6H).

Intermediate 154-[(3,5-Bis-trifluoromethyl-benzyl)-methyl-carbamoyl]-3-(2-isopropyl-phenyl)-piperazine-1-carboxylic acid benzyl ester.

To a solution of intermediate 10 (46 mg) in anh. CH_2Cl_2 (3.9 mL), at 0°C, under N_2 , triethylamine (145 μL) was added. To this solution a solution of triphosgene (46 mg) in anh. CH_2Cl_2 (3 mL) was added drop-wise. The reaction was stirred at 0°C for 2 hr.

To this solution diisopropylethylamine (121 μL) and (3,5-bis-trifluoromethyl-benzyl)-methyl-amine hydrochloride (122 mg) were added. The solution was stirred at r.t. for 18 hr. The reaction mixture was diluted with CH_2Cl_2 , washed with 10% citric acid (1x) and dried over Na_2SO_4 . The solids were filtered and the solvent evaporated. The crude oil was purified by flash chromatography. The title compound was obtained as a clear oil (108 mg).

NMR (CDCl_3): δ (ppm) 7.89 (bs, 1H), 7.71 (bs, 2H), 7.38-7.28 (m, 5H), 7.28 (dd, 1H), 7.23 (dd, 1H), 7.16 (dt, 1H), 7.01 (dt, 1H), 5.14 (d, 1H), 5.05 (bd, 1H), 4.68 (dd, 1H), 4.52 (2d(AB), 2H), 3.83 (dd, 1H), 3.71 (dt,

1H), 3.53 (md, 1H), 3.41 (dt, 1H), 3.26 (m, 1H), 3.15-3.05 (m, 2H), 1.19 (d, 3H), 1.13 (m, 3H).

Intermediate 16

5 **4-[(3,5-Bis-trifluoromethyl-benzyl)-methyl-carbamoyl]-3-(4-fluoro-3-methyl-phenyl)-piperazine-1-carboxylic acid benzyl ester**

To a solution of intermediate 11 (170 mg) in anh. CH_2Cl_2 (7 mL), at 0°C, under N_2 , triethylamine (217 μL) was added. To this solution a solution of triphosgene (69 mg) in anh. CH_2Cl_2 (3 mL) was added drop-wise. The 10 reaction was stirred at 0°C for 2 hr.

To this solution diisopropylethylamine (181 μL) and (3,5-bis-trifluoromethyl-benzyl)-methyl-amine hydrochloride (183 mg) were added. The solution was stirred at r.t. for 18 hr. The reaction mixture was diluted with CH_2Cl_2 , washed with 10% citric acid (1x) and dried over Na_2SO_4 . 15 The solids were filtered and the solvent evaporated. The crude oil was purified by flash chromatography. The title compound was obtained as a gummy solid (226mg).

20 NMR (CDCl_3): δ (ppm) 7.77 (m, 1H), 7.60 (m, 2H), 7.3-7.4 (m, 5H), 7.05-7.15 (m, 2H), 6.90 (m, 1H), 5.14 (m, 2H), 4.6-4.8 (m, 1H), 4.54 + 4.47 (AB, 2H), 3.82 (bm, 1H), 3.73 (dd, 1H), 3.65 (m, 1H), 3.57 (m, 1H), 3.33 (m, 1H), 3.26 (m, 1H), 2.90 (s, 3H), 2.19 (s, 3H).

Intermediate 17

25 **4-[(3,5-Bis-trifluoromethyl-benzyl)-methyl-carbamoyl]-3-(2,4-difluoro-phenyl)-piperazine-1-carboxylic acid benzyl ester**

To a solution of intermediate 12 (95 mg) in anh. CH_2Cl_2 (3 mL), at 0°C, under N_2 , triethylamine (120 μL) was added. To this solution a solution of triphosgene (38mg) in anh. CH_2Cl_2 (3 mL) was added drop-wise. The reaction was stirred at 0°C for 2 hr.

30 To this solution diisopropylethylamine (100 μL , 2 eq) and (3,5-bis-trifluoromethyl-benzyl)-methyl-amine hydrochloride (101mg) were added. The solution was stirred at r.t. for 18 hr. The reaction mixture was diluted with CH_2Cl_2 , washed with 10% citric acid (1x) and dried over Na_2SO_4 . The solids were filtered and the solvent evaporated. The crud oil was 35 purified by flash chromatography. The title compound was obtained as a yellow gum (134mg).

NMR (CDCl₃): δ (ppm) 7.76 (s, 1H), 7.56 (s, 2H), 7.26-7.40 (m, 6H), 6.76 (m, 2H), 5.17 (m, 2H), 4.83 (m, 1H), 4.36-4.60 (dd + m, 2H), 3.90 (m, 1H), 3.25-3.7 (m, 2H), 2.86 (s, 3H).

5 Intermediate 18

4-(3,5-bis(trifluoromethyl)-benzyl-carbamoyl)-3-(4-fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid benzyl ester

To a solution of intermediate 8 (0.15g) and triethylamine (0.32ml) in CH₂Cl₂ (35ml), a solution of triphosgene (0.065ml) in CH₂Cl₂ (25ml) was added drop-wise at 0° C. The reaction mixture was allowed to warm to r.t. in 3 hr, then pyridine (0.3ml) and 3,5-bis(trifluoromethyl)benzyl-1-methyl-amine hydrochloride (53mg) were added. The reaction mixture was stirred at r.t. overnight, then washed with a 1N solution of HCl and brine. The organic phase was next dried with Na₂SO₄ and concentrated to give the crude product which was purified by flash column chromatography to obtain the title compound (0.086g) as a pale yellow oil and 4-benzyloxycarbonyl-2-(4-fluoro-2-methyl-phenyl)-piperazine-1-carbonyl chloride (0.075g).

20 Title compound: NMR (CDCl₃) δ (ppm) .78-7.7 (m, 1H), 7.5-7.4 (m, 2H), 7.4-7.25 (m, 5H), 7.20 (m, 1H), 6.95-6.8 (m, 2H), 5.2-5.05 (m, 2H), 4.99 (dd, 1H), 4.6-4.2 (m, 2H), 4.5-4.15 (m, 2H), 3.8-3.6 (m, 2H), 4.12 (m, 1/2H), 3.91 (m, 1/2H), 3.61 (m, 1/2H), 3.44 (m, 1/2H), 2.4-2.2 (s+s, 3H).

25 Intermediate 19

3-(4-Fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid 1-(S)-phenyl-ethyl ester

To a solution of 1,1'carbonyldiimidazole (0.162g) in CH₂Cl₂ (5ml) (S)-sec-Phenethyl alcohol (0.122g) was added. After 30 min. a solution of intermediate 7 (0.180g) in CH₃CN (5ml) was added and the mixture refluxed for 2 hr. Then the mixture was concentrated to give the crude product which was purified by flash chromatography (cyclohexane ethyl acetate 80: 20) to obtain the title compound (mix diastereomer) (0.180g) as a foam.

35 NMR (DMSO) δ (ppm) 7.87 (m, 1H); 7.40-7.25 (m, 5H); 7.02-6.94 (m, 2H); 5.74 (m, 1H); 3.93-3.71 (m, 3H); 3.00-2.55 (m, 4H); 2.34 (s, 3H); 2.28 (s, 3H)

Intermediate 20

4-(3,5-bis-trifluoromethyl-benzyl-carbamoyl)-3-(4-fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid 1-(S)-phenyl-ethyl ester (diastereomer 1) (20a)

4-(3,5-bis-trifluoromethyl-benzyl-carbamoyl)-3-(4-fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid 1-(S)-phenyl-ethyl ester (diastereomer 2) (20b)

5 To a solution of intermediate 19 (0.180g) and triethylamine (0.35ml) in CH₂Cl₂ (5 ml) a solution of triphosgene (0.075g) in CH₂Cl₂ (5ml) was added drop-wise at 0° C. After 2 hr, diisopropylethylamine (0.3ml) and (3,5-bistrifluoromethylbenzyl)-methyl-amine hydrochloride (0.209g) were added and the mixture was warmed at r.t. After 4 hr CH₂Cl₂ was added and the organic phase was washed with HCl 1N (2 x 10ml) and brine, 10 dried with Na₂SO₄ and concentrated to give the crude diastereoisomeric mixture. Separation by flash chromatography (silica gel, 8:2 cHex/EtOAc) 15 yielded the title compound 20a (0.125g) and the title compound 20b (0.135g) as white foams.

20 Intermediate 20a NMR (DMSO) δ (ppm) 7.90 (s, 1H); 7.67 (s, 2H); 7.4-7.27 (m, 6H); 6.95 (dd, 1H); 6.80 (m, 1H); 5.74 (q, 1H); 4.60-4.40 (dd, 2H); 4.50 (m, 1H); 3.79 (m, 3H); 3.00 (m, 3H); 2.87 (s, 3H); 2.29 (s, 3H); 1.46 (d, 3H).

25 Intermediate 20b NMR (DMSO) δ (ppm) 7.90 (s, 1H); 7.67 (s, 2H); 7.37-7.24 (m, 6H); 6.95 (dd, 1H); 6.81 (m, 1H); 5.75 (q, 1H); 4.60-4.41 (dd, 2H); 4.52 (m, 1H); 3.83-3.00 (m, 6H); 2.88 (s, 3H); 2.33 (s, 3H); 1.48 (d, 3H).

Intermediate 21

[1-(2,4-bis-trifluoromethyl-phenyl)-ethyl]-methyl-amine

30 To a 2 M solution of MeNH₂ in MeOH (10 ml) commercial 3,5-Bis(trifluoromethyl)acetophenone (2.1g) was added. After 12 hr the mixture was cooled at 0° C and then NaBH₄ (0.512g) was added. After 1 hr the mixture was quenched with H₂O and extracted with CH₂Cl₂. Then the organic phase was dried with Na₂SO₄ and concentrated to give the 35 crude product which was purified by distillation to obtain the title compound (1.5g) as an oil.

NMR (CDCl₃) δ (ppm) 7.8 (m, 3H); 3.8 (q, 1H); 2.4 (s, 3H); 1.4 (d, 3H)

Intermediate 22

4-[{1-(3,5-bis-trifluoromethyl-phenyl)-ethyl}-methyl-carbamoyl]-3-(4-fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid benzyl ester (mixture of enantiomers AB) (22a)

4-[{1-(3,5-bis-trifluoromethyl-phenyl)-ethyl}-methyl-carbamoyl]-3-(4-fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid benzyl ester (mixture of enantiomers C,D)(22b)

10 To a solution of 4-benzyloxycarbonyl -2-(4-fluoro-2-methyl-phenyl)-piperazine-1-carbonyl chloride (0.075g) in CH₂Cl₂ (5 ml) diisopropylethylamine (0.12ml) and intermediate 21 (0.1g) were added. The mixture was refluxed for 2 hr, then CH₃CN (5ml) was added and the obtained solution was heated 70°C and the mixture was stirred overnight.

15 Then the mixture was concentrated and the residue was dissolved in ethylacetate. The organic phase was washed with HCl 1N and brine and dried with Na₂SO₄. Then the organic phase was concentrated to give the crude mixture of diastereomeric compounds which were separated by flash chromatography (silica gel, 8:2 cHex/EtOAc) to obtain intermediate

20 22a (0.05g) and intermediate 22b (0.55g) as white foams.

Intermediate 22a NMR (CDCl₃) δ (ppm) 7.78 (s, 1H); 7.58 (s, 2H); 7.4-7.3 (m, 5H); 7.18 (m, 1H); 6.86 (m, 1H); 6.77 (m, 1H); 5.45 (m, 1H); 5.16 (s, 2H); 4.6 (m, 1H); 3.94 (m, 2H); 3.44-3.10 (m, 4H); 2.68 (s, 3H); 2.4 (s, 3H); 1.49 (d, 3H).

25 Intermediate 22b NMR (CDCl₃) δ (ppm) 7.75 (s, 1H); 7.53 (s, 2H); 7.4-7.3 (m, 5H); 7.18 (m, 1H); 6.87 (m, 1H); 6.78 (m, 1H); 5.59 (m, 1H); 5.18 (s, 2H); 4.59 (m, 1H); 3.97 (m, 2H); 3.44-3.06 (m, 4H); 2.78 (s, 3H); 2.37 (s, 3H); 1.53 (d, 3H).

30 **Intermediate 23**

(4-Fluoro-2-methyl-phenyl)-oxo-acetic acid methyl ester

1) To a suspension of magnesium turnings (617 mg) in anh. THF (6 mL), at r.t., under N₂, a small crystal of I₂ was added, followed by a solution of commercial 2-bromo-5-fluorotoluen (4.0g) in anh. THF (15 mL). The suspension was heated gently (heat gun) until the brown colour disappeared. The rest of the bromide solution was added drop-wise,

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maintaining the reaction mixture warm (50-60°C) with an oil bath. After the addition was complete (15 min) the suspension was stirred at 70°C until the magnesium turnings had almost completely reacted (2 hr). The new brown solution was used in the next step.

5 2) A solution of LiBr (4.41 g) in anh. THF (50 mL) was added drop-wise to a suspension of CuBr (3.64g) in anh. THF (50 mL). The reaction mixture was stirred at r.t. for 1 hr (dark green solution with a small amount of white solid in suspension). The Grignard solution prepared above was then added drop-wise (an ice bath was used to maintain the temperature

10 <25°C) followed by methyl oxalyl chloride (1.95 mL). The reaction mixture was stirred at r.t. for 2 hr. The THF was evaporated and the residue was taken up in EtOAc. The organic layer was washed with sat.aq. NH₄Cl (2x) and dried over Na₂SO₄. The solids were filtered and the solvent evaporated to give a crude oil, which was purified by flash

15 chromatography to obtain the title compound as a clear oil (2.44g).
NMR (CDCl₃): δ (ppm) 7.74 (m, 1H), 6.98-7.04 (m, 2H), 3.96 (s, 3H), 2.61 (s, 3H).

Intermediate 24

(4-Fluoro phenyl)-oxo- acetic acid methyl ester

20 To magnesium turnings (0.066 g), previously heated at 90 °C and covered by THF (1ml), a crystal of iodine was added followed by a solution of commercial 4-Fluoro-bromobenzene (0.437g) in THF (4ml). The temperature was kept at 60°C till the consumption of the metal. The

25 solution of the organometallic derivative was added drop-wise on a solution of CuBr (0.356 g) and LiBr (0.431g) in THF (10ml), previously prepared at 0°C.

At the end of the addition methyl oxalyl chloride (0.225ml) was added via syringe and the reaction mixture was stirred 2h at r.t, before being poured into an aqueous saturated solution of NH₄Cl and extracted with Et₂O. The organic phase was washed with brine and dried on Na₂SO₄. The crude product obtained after evaporation of solvents was purified by column chromatography affording the title compound (0.2g) as a solid.
1H-NMR (CDCl₃): δ (ppm): 8.12 (m, 2H), 7.20 (m, 2H), 3.99 (s, 3H).

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Intermediate 25

3-(4-Fluoro-2-methyl-phenyl)-5,6-dihydro-1H-pyrazin-2-on

To a solution of intermediate 23 (2.01g) and ethylene diamine (684 μ L) in toluene (40 mL), at r.t., under N_2 , anh. Na_2SO_4 (2g) was added. The reaction mixture was heated at reflux for 6 hr. It was then cooled down to r.t. and filtered. The solids were rinsed with CH_2Cl_2 . The solvent was evaporated and the crude oil was purified by flash chromatography affording the title compound as a white solid (1.29g).

1H -NMR ($CDCl_3$): δ (ppm) 7.33 (m, 1H), 6.95-6.90 (m, 2H), 6.56 (m, 1H), 3.97 (m, 2H), 3.58 (m, 2H), 2.31 (s, 3H).

10 **Intermediate 26**

3-(4-Fluoro-phenyl)-5,6 dihydro-1H-pyrazin-2-one

Intermediate 24 (0.190g) was dissolved in dry toluene (5ml) under inert atmosphere; ethylendiammine (0.072ml) was added drop-wise followed by Na_2SO_4 (0.2g) and the reaction mixture was refluxed 2 hr. The solids were filtered off and the crude product obtained after evaporation of the solvent was purified by flash chromatography affording the title compound (0.155g as a white solid).

mp 118-120°C

1H -NMR ($CDCl_3$) δ (ppm): 7.96 (m, 2H), 7.08 (m, 2H), (bs, 1H), 3.96 (t, 2H), 3.54 (m, 2H).

Intermediate 27

Bromo-(2,4-dichloro-phenyl)-acetic acid methyl ester.

To a stirred solution of commercial 2,4-dichlorophenylacetic acid (2g) in CH_2Cl_2 (50ml) DMF (0.1ml) and oxalyl chloride (1.7ml) were added and the reaction mixture was heated at reflux for 1 $\frac{1}{2}$ hr. The solvent was evaporated and the crude compound was dissolved in carbon tetrachloride (40ml). N-bromosuccinimide (1.8g) and 2,2'-azobis(2-methylpropionitrile) (0.1g) were added and the reaction mixture was heated at reflux and irradiated for 2 hr. After cooling, methanol (50ml) was added and the reaction mixture was stirred for 1 hr. The solution was concentrated, diluted with ethyl acetate and washed with a 3N HCl and brine. The organic phase was next dried with Na_2SO_4 and concentrated to give a crude residue which was purified by flash column chromatography to obtain a mixture of the title compound and 2,4-dichlorophenyl-acetic acid, m thyl ester (1.3g).

This mixture was dissolved in carbon tetrachloride (20ml) then N-bromosuccinimide (0.89g) and 2,2'-azobis(2-methylpropionitrile) (0.05g) were added and the reaction mixture was heated at reflux and irradiated for 3 1/2 hr. The solution was concentrated, diluted with ethyl acetate and washed with a saturated solution of Na_2CO_3 and brine. The organic phase was next dried with Na_2SO_4 and concentrated to give a crude residue which was purified by flash column chromatography to yield the title compound (1.14g, pale yellow oil).

5 NMR (CDCl_3): δ (ppm) 7.72 (d, 1H), 7.40 (d, 1H), 7.30 (dd, 1H), 5.84 (s, 1H), 3.81 (s, 3H)

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Intermediate 28

Bromo-(3,4-dichloro-phenyl)-acetic acid methyl ester.

To a stirred solution of commercial 3,4-dichlorophenylacetic acid (2g) in CH_2Cl_2 (100 ml) DMF (0.1ml) and oxalyl chloride (1.7ml) were added and the reaction mixture was heated at reflux for 1 1/2 hr. After cooling, methanol (50ml) was added and the reaction mixture was stirred for 1 hr. The solvent was evaporated and the crude compound was purified by flash column chromatography to obtain the methyl ester that was dissolved in carbon tetrachloride (60ml). N-bromosuccinimide (2.06g) and 2,2'-azobis(2-methylpropionitrile) (0.2g) were added and the reaction mixture was heated at reflux and irradiated for 2hr. The solution was concentrated, diluted with ethyl acetate and washed with a saturated solution of Na_2CO_3 and brine. The organic phase was next dried with Na_2SO_4 and concentrated to give a crude residue which was purified by flash column chromatography to obtain the title compound (2.0g) as an oil.

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NMR (CDCl_3) δ (ppm) 7.70 (s, 1H), 7.45 (m, 1H), 5.25 (s, 1H), 3.80 (s, 3H)

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Intermediate 29

3-(2,4-dichloro-phenyl)-piperazine-2-one.

To a solution of intermediate 27 (1.14g) in EtOH (20ml) sodium ethoxide (0.34g) and ethylenediamine (0.54ml) were added and the reaction mixture was stirred at r.t. for 15 hr. The solvent was evaporated and the residue was purified by flash column chromatography to yield the title compound (0.35g, white foam).

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NMR (DMSO): δ (ppm) 7.87 (broad, 1H), 7.55 (d, 1H), 7.41, 7.37 (d+dd, 2H), 4.63 (s, 1H), 3.32, 3.14 (m+m, 2H), 3.02-2.90, 2.84 (m+m, 3H).

Intermediate 30

5 **3-(3,4-dichloro-phenyl)-piperazine-2-one.**

To a solution of intermediate 28 (2.0g) in EtOH (100ml) sodium ethoxide (0.60g) and ethylenediamine (0.95ml) were added and the reaction mixture was stirred at r.t. for 15 hr. The solvent was evaporated and the residue was diluted with ethyl acetate and washed with brine. The 10 organic phase was next dried with Na_2SO_4 and concentrated to give a crude residue which was purified by flash column chromatography to yield the title compound (2.0g, white foam).

NMR (CDCl_3): δ (ppm) 7.60 (d, 1H), 7.42 (d, 1H), 7.32, (dd, 1H), 5.91 (sa, 1H), 4.53 (s, 1H), 3.6-3.1 (m+m, 4H).

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Intermediate 31

3-Oxo-2-phenyl-piperazine-1-carbonyl chloride

To a stirred solution of triphosgene (0.558g) in CH_2Cl_2 (10ml) pyridine (0.46ml) was added at 0°C and, after 10 min, 3-phenyl-piperazine-2-one (1g). The ice bath was removed and the mixture was stirred at room 20 temperature overnight. The mixture was concentrated and the product was purified by flash chromatography to give the title compound (0.253g) as a foam.

NMR (CDCl_3): δ (ppm): 7.45-7.35 (m, 5H); 6.81 (bs, 1H); 6.61 (bs, 1H); 25 5.99 (s, 1H); 4.3-4.2 (m, 1H); 3.7-3.3 (m, 3H)

Intermediate 32

2-(4-Fluoro-2-methyl-phenyl)-3-oxo-piperazine-1-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide

30 To a solution of intermediate 25 (63mg) in anh. CH_3OH (6.1 mL), at r.t., under N_2 , Pd/C 10% (7 mg, 10% wt) was added. The reaction mixture was placed under an H_2 atmosphere and was stirred at r.t. for 2 hr. The catalyst was filtered (filtering paper) and the solvent was evaporated. The crude 3-(4-Fluoro-2-methyl-phenyl)-piperazin-2-one (64mg) was 35 dried under high vacuum and dissolved in anh. CH_2Cl_2 (4.0 mL), at 0°C, under N_2 , and Et_3N (85 μL) was added. To this solution, a solution of

5 triphosgene (37 mg) in anh. CH_2Cl_2 (2 mL) was added drop-wise. The reaction was stirred at 0°C for 2 hr. To this solution iPr_2NEt (107 μL) and N-methyl-bis(trifluoromethyl)-benzylamine hydrochloride (108 mg) were added. The solution was stirred at r.t. for 18 hr. The reaction mixture was diluted with CH_2Cl_2 , washed with 1N HCl (1x) and dried over Na_2SO_4 . The solids were filtered and the solvent evaporated. The crude product was purified by flash chromatography. The title compound was obtained as a white solid (93mg).

10 NMR (CDCl_3): δ (ppm) 7.79 (s, 1H), 7.59 (s, 2H), 7.20 (bs, 1H), 6.91-6.84 (m, 1H), 6.07 (m, 1H), 5.69 (s, 1H), 4.58-4.47 (dd, 1H), 3.49 (m, 4H), 2.85-2.39 (s, 6H).

Intermediate 33

2-(4-Fluoro-phenyl)-3-oxo-piperazine-1-carboxylic acid (3,4-bis-trifluoromethyl-benzyl)-methyl-amide

15 Intermediate 26 (0.135g) was dissolved in CH_3OH (5ml) and the temperature lowered at 0°C, then NaBH_4 (0.102g) was carefully added. After 2 hr the reduction was complete, the solvent was removed under reduced pressure and CH_2Cl_2 was added. The organic phase was washed with H_2O and brine before being dried on Na_2SO_4 . The crude 3-(4-Fluoro-phenyl)-piperazin-2-one (0.140g) was dried under high 20 vacuum and dissolved in anhydrous CH_2Cl_2 (5ml), at 0°C and triethylamine (0.433ml) was added drop-wise. To this solution a solution of triphosgene (0.09g) in dry CH_2Cl_2 (3ml) was added at 0°C, under inert 25 atmosphere. The temperature was maintained at 0°C for 3 hr, then diisopropylethylamine (0.4ml) followed by 3,5-bistrifluoromethyl-methyl-amine hydrochloride (0.27g) were added. The reaction mixture was stirred at r.t. overnight before being diluted with CH_2Cl_2 and washed with a 1N solution of HCl, H_2O and brine in sequence. The organic phase was dried on Na_2SO_4 and the crude product obtained after evaporation of the 30 solvent was purified by flash column chromatography affording the title compound as a foam (0.2g).

35 NMR (DMSO): δ (ppm) 8.14 (bs, 1H), 7.97 (s, 1H), 7.78 (s, 2H), 7.37 (2H, m), 7.09 (m, 2H), 5.13 (s, 1H), 4.49 (dd, 2H), 3.5-3.25 (4H, m), 2.80 (3H, s).

Intermediate 34

3-Oxo-2-phenyl-piperazine-1-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide

To a stirred solution of intermediate 31 (0.239g) in DMF (5ml) diisopropylethylamine (0.41ml) and 3,5-bistrifluoromethyl-methyl-amine

5 hydrochloride (0.366g) were added. After 3 hr the mixture was quenched with brine and the aqueous layer was extracted with ethyl acetate. The organic layer was dried (Na_2SO_4) and concentrated at reduced pressure. The product was purified by flash chromatography to give the title compound (0.429g).

10 NMR (CDCl_3): δ (ppm): 7.79(bs, 1H); 7.67(bs, 2H); 7.50(d, 2H); 7.35(m, 3H); 5.98(s, 1H); 5.43(s, 1H); 4.63-4.32(dd, 2H); 3.88-3.56(m, 2H); 3.50-3.30(m, 2H); 2.81(s, 3H);

Intermediate 35

15 **2-(2,4-dichloro-phenyl)-3-oxo-piperazine-1-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide.**

To a solution of intermediate 29 (0.33g) in CH_2Cl_2 (30ml) triethylamine (0.65ml) and, drop-wise, a solution of triphosgene (0.23g) in CH_2Cl_2 (10ml) were added. The reaction mixture was stirred at r.t. for 1 $\frac{1}{2}$ hr then 20 concentrated and purified by flash column chromatography to yield 2-(2,4-dichloro-phenyl)-3-oxo-piperazine-1-carbonyl chloride (0.3g, white foam). The latter was dissolved in CH_2Cl_2 (30ml), then diisopropylethylamine (0.3ml) and (3,5-bistrifluoromethylbenzyl)-methyl-amine hydrochloride (0.32g) were added. The reaction mixture was 25 stirred at reflux for 3 hr, then washed with a 1N solution of HCl and brine. The organic phase was next dried with Na_2SO_4 and concentrated to give the crude product which was purified by flash column chromatography to obtain the title compound (0.45g, white foam).

30 NMR (DMSO) δ (ppm) 8.30 (bs, 1H), 7.96 (bs, 1H), 7.73 (bs, 1H), 7.54 (d, 1H), 7.35, 7.33 (d+dd, 2H), 5.44 (s, 1H), 4.61 (d, 1H), 4.39 (d, 1H), 3.39, 3.25 (m+m, 4H), 2.76 (s, 3H).

Intermediate 36

35 **2-(3,4-dichloro-phenyl)-3-oxo-pip razin -1-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide.**

To a solution intermediate 30 (0.413g) in CH_2Cl_2 (40ml) triethylamine (1.4ml) and, drop-wise, a solution of triphosgene (0.25g) in CH_2Cl_2 (10ml) was added. The reaction mixture was stirred at r.t. for 1 $\frac{1}{2}$ hr, then diisopropylethylamine (0.6ml) and (3,5-bistrifluoromethylbenzyl)-methylamine hydrochloride (0.54g) were added. The reaction mixture was stirred at reflux for 3hr, then washed with a 1N solution of HCl and brine. The organic phase was next dried with Na_2SO_4 and concentrated to give the crude product which was purified by flash column chromatography to obtain the title compound (0.13g, white foam).

10 NMR (DMSO) δ (ppm) 8.24 (bs, 1H), 7.96 (s, 1H), 7.75 (s, 2H), 7.54 (d, 1H), 7.51(d,1H), 7.33 (dd, 1H), 5.11 (s, 1H), 4.49 (dd, 2H), 3.5- 3.25 (m+m, 4H), 2.82 (s, 3H).

Intermediate 37

15 4-(3,5-bis-trifluoromethyl-benzyl-carbamoyl)-3-(4-fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid 1-(R)-phenyl-ethyl ester (diastereomer 1) (37a)

4-(3,5-bis-trifluoromethyl-benzyl-carbamoyl)-3-(4-fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid 1-(R)-phenyl-ethyl ester (diastereomer 2) (37b)

20 To a solution of carbonyl diimidazole (402mg) in CH_2Cl_2 (8.3ml), at r.t., under N_2 , (R)-sec-phenylethyl alcohol (0.3 mL) was added. The solution was stirred at r.t. for 1 hr. Example 11(790mg) in anh. CH_3CN (8.3 mL) was then added to the solution and the reaction mixture was heated at 25 50°C without a water condenser in order to evaporate the CH_2Cl_2 . A water condenser was then adjusted to the flask and the reaction mixture was refluxed for 4 hr. The solvent was then evaporated and the residue partitioned between EtOAc/1N HCl. The phases were separated and the organic layer was washed with sat. aq. NaCl (2x). It was then dried over Na_2SO_4 , the solids were filtered and the solvent evaporated. The crude oil was purified by flash chromatography (silica gel, 8:2 cHex/EtOAc). The mixed fractions were re-chromatographed using the same conditions.

30 Intermediates 37a (242 mg) and 37b (152mg) were obtained as white foams.

35

Intermediat 37a

NMR (DMSO) δ (ppm): 7.90 (s, 1H); 7.67 (s, 2H); 7.37-7.24 (m, 6H); 6.95 (dd, 1H); 6.81 (m, 1H); 5.75 (q, 1H); 4.60-4.41 (dd, 2H); 4.52 (m, 1H); 3.83-3.00 (m, 6H); 2.88 (s, 3H); 2.33 (s, 3H); 1.48 (d, 3H).

5 Intermediate 37b

NMR (DMSO) δ (ppm): 7.90 (s, 1H); 7.67 (s, 2H); 7.4-7.27 (m, 6H); 6.95 (dd, 1H); 6.80 (m, 1H); 5.74 (q, 1H); 4.60-4.40 (dd, 2H); 4.50 (m, 1H); 3.79 (m, 3H); 3.00 (m, 3H); 2.87 (s, 3H); 2.29 (s, 3H); 1.46 (d, 3H).

10 Intermediate 38

4-[1-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methyl-carbamoyl]-3-(4-fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid 1-(S)-phenyl-ethyl ester (diastereoisomer 1) (38a)

4-[1-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methyl-carbamoyl]-3-(4-

15 fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid 1-(S)-phenyl-ethyl ester (diastereoisomer 2) (38b)

To a solution of 1,1'Carbonyldiimidazole (0.163 g) in CH_2Cl_2 (5ml) (R)-sec-Phenethyl alcohol (0.122g) was added and the mixture was stirred at room temperature for 30 min. Then a solution of 2-(4-fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid [1-(3,5-bis-trifluoromethyl-phenyl)ethyl]-methyl-amide (0.250g) in CH_3CN (5ml) was added and the mixture was refluxed for 4 hr. The mixture was cooled and ethyl acetate was added. The organic phase was washed with HCl 1N (2 X 50 ml) and brine, dried with Na_2SO_4 and concentrated to give the crude mixture of diastereoisomers which were separated by flash chromatography (silica gel, 8:2 cHex/EtOAc) to obtain the title compound 38a (diastereomer 1) (0.08g) and the title compound 38b (diastereomer 2)(0.08g).

20 Intermediate 38a: NMR (CDCl_3) δ (ppm) 7.74 (s, 1H); 7.52 (s, 2H); 7.40-7.24 (m, 5H); 7.18 (m, 1H); 6.87 (m, 1H); 6.80 (m, 1H); 5.86 (q, 1H); 5.57 (q, 1H); 4.7-4.46 (m, 1H); 3.98 (m, 2H); 3.44-2.96 (m, 4H); 2.77 (s, 3H); 2.36 (s, 3H); 1.54 (m, 6H).

25 Intermediate 38b NMR (CDCl_3) δ (ppm) 7.74 (s, 1H); 7.53 (s, 2H); 7.40-7.26 (m, 5H); 7.16 (m, 1H); 6.87 (m, 1H); 6.78 (m, 1H); 5.86 (q, 1H); 5.57 (m, 1H); 4.62 (m, 1H); 4.04 (m, 1H); 3.84 (m, 1H); 3.50-3.04 (m, 4H); 2.76 (s, 3H); 2.41 (s, 3H); 1.56 (m, 6H).

Intermediate 39**(+)-3-(4-Fluoro-2-methyl-phenyl)-piperazin-2-one.**

5 To a suspension of Intermediate 25 (35g) in AcOEt (900ml), L(+)-Mandelic Acid (27.3g) was added. The suspension was stirred at r.t for 1 hr then at 3-5°C for 2 hr filtered and dried under vacuum at r.t to obtain crude L(+)-mandelate 3-(4-Fluoro-2-methyl-phenyl)-piperazin-2-one (37g) which was suspended in Ethyl Acetate (370ml) and heating to reflux till complete solubilisation then cooled to room temperature and stirred for further 2 hours, filtered and washed with of Ethyl Acetate (150ml) dried under vacuum obtaining (+) L-mandelate 3-(4-Fluoro-phenyl)-5,6 dihydro-1H-pyrazin-2-one (30.4g) as white solid. (+) L-mandelate 3-(4-Fluoro-phenyl)-5,6 dihydro-1H-pyrazin-2-one (30.4g) was suspended in Ethyl Acetate (300ml) and treated with NaOH (0.73M 10 155ml) saturated with NaCl. The organic phase was then washed with water (90ml).

10 The aqueous phase was counter-extracted 4 times with ethyl acetate (90ml). The combined organic phase (1800ml) was dried on 10g of Na₂SO₄ and concentrated under vacuum obtaining the title compound (25.04g) as white foam.

15 HPLC: Chiralcel OJ (4.6X250mm) from Daicel; Mobile Phase:n-Hxane/Ethanol 80/20 v/v; Flow:1 mL/min; Detector:UV @ 265nm (or 210 nm for higher signals); Dissolutin phase:n-Hxane/Ethanol 80/20 v/v; Sample Concentration 1 mg/ml; Injection:5uL; Retention times: 2:8.4 min. 20 [α]D(solvent CHCl₃, Source.: Na⁺; Cell volume [ml] : 1; Cell pathlength [dm]:1; Cell temperature [°C]:20; Wavelength [nm] : 589; Conc. sample [% p/v] :1.17)=+17.9.

Intermediate 40

25 30 2-(4-Fluoro-2-methyl-phenyl)-3-oxo-piperazine-1-carboxylic acid [1-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methyl-amide.(diastereoisomer 1)(40a)
 2-(4-Fluoro-2-methyl-phenyl)-3-oxo-piperazine-1-carboxylic acid [1-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methyl-amide.(diastereoisomer 2)(40b)

To a solution of intermediate 39 (12.1g) in anhydrous CH_2Cl_2 (270ml), Et₃N (16.4ml) was added. The solution was cooled down to 0°C and a solution of triphosgene (7.3g) in anh. CH_2Cl_2 (60ml) was added drop-wise over 40 min. The reaction mixture was stirred at 0°C for 4 hr and was brought back to r.t.. iPr₂NEt (20.2ml) was then added, followed by a solution of [1-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methyl-amine (23.6g) in CH_3CN (300ml) and an additional 300ml of CH_3CN . The reaction mixture was warmed up to 95°C (oil bath T°C) without a water condensor to evaporate the CH_2Cl_2 . When the intern temperature had reached 10 70°C, the flask was equipped with a water condenser, and the reaction mixture was heated at 70°C for an additional 2 hr (4 hr total). It was then brought back to r.t. and the solvent was evaporated. The residue was partitioned between CH_2Cl_2 /2% HCl and the phases were separated. The aqueous layer was extracted with CH_2Cl_2 (1x) and the combined 15 organic extracts were dried over Na_2SO_4 . The solids were filtered and the solvent evaporated to give a crude mixture of title compounds which were purified by flash chromatography (silica gel, EtOAc/cyclohexane 8/2) to obtain the title compounds 40a (8.8g) and 40 b (9.0g) as white foams.

20 **Intermediate 40a**

25 **NMR (¹H, DMSO-d₆):** δ 8.16 (s, 1H), 7.98 (s, 2H), 7.19 (dd, 1H), 6.97 (dd, 1H), 6.87 (td, 1H), 5.34 (s, 1H), 5.14 (q, 1H), 3.45-3.2 (m, 4H), 2.53 (s, 3H), 2.27 (s, 3H), 1.56 (d, 3H).

30 **Intermediate 40b**

35 **NMR (¹H, DMSO-d₆):** δ 8.16 (s, 1H), 7.95 (s, 2H), 7.19 (dd, 1H), 6.98 (dd, 1H), 6.90 (td, 1H), 5.29 (q, 1H), 5.28 (s, 1H), 3.45-3.15 (m, 4H), 2.66 (s, 3H), 2.27 (s, 3H), 1.52 (d, 3H).

40 **Intermediate 41**

45 **4-[2-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-ethyl]-2-(4-fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide**

50 To a solution of example 8 (0.05g) in anhydrous DMF (1ml), under N_2 , at room temperature, were added triethylamine (40 μl) and N-(2-bromoethyl)-phthalimid (28mg). The reaction mixture was stirred at 80°C for 5 hr and was then cooled down to room temperature. It was poured in sat.aq. NaCl and the phases were separated. The organic

layer was washed with sat. aq. NaCl (2x) and dried over Na_2SO_4 . The solids were filtered and the solvent evaporated. The crude product was purified by flash chromatography to give the title compound (0.25g) as a yellow oil.

5 NMR (DMSO) δ (ppm) 7.94 (s, 1H), 7.80-7.90 (m, 4H), 7.67 (s, 2H), 7.33 (m, 1H), 6.91 (dd, 1H), 6.45 (td, 1H), 4.60 (d, 1H), 4.34 (m, 2H), 3.80 (m, 1H), 3.64 (m, 1H), 3.18 (m, 1H), 2.82 (s, 3H), 2.79 (m, 1H), 2.80 (m, 1H), 2.66 (m, 1H), 2.60 (m, 2H), 2.46 (m, 1H), 2.26 (m, 1H), 2.27 (s, 3H).
 10 IR (Nujol) (cm^{-1}) 1650 – 1773.
 10 MS (*m/z*) 651 [MH], 673 [M+Na]⁺.

Intermediate 42

1-(4-Fluoro-2-methyl-phenyl)-propane-1,2-dione

15 1) To a suspension of magnesium turnings (283mg) in anh. THF (3 mL), at r.t., under N_2 , was added a small crystal of I_2 , followed by 10% of a solution of 1-bromo-4-fluoro-2-methyl-benzene (2.0g) in anhydrous THF (8 mL). The suspension was heated gently (heat gun) until the brown colour disappeared. The rest of the bromide solution was added drop-wise, maintaining the reaction mixture warm (50-60°C) with an oil bath.
 20 After the addition was complete (15 min) the suspension was stirred at 70°C until the magnesium turnings had almost completely reacted (2 hr). The new brown solution was used in the next step.
 25 2) A solution of LiBr (2.26g) in anh. THF (26 mL) was added drop-wise a suspension of CuBr (1.82 g) in anh. THF (26 mL). The reaction mixture was stirred at r.t. for 1 hr. The reaction mixture was then brought at -78°C and the Grignard solution prepared above was added dropwise followed by pyruvyl chloride (1.13g). The reaction mixture was stirred at -78°C for 2 hr. The THF was evaporated and the residue was taken up in EtOAc. The organic layer was washed with sat.aq. NH_4Cl (2x) and dried over Na_2SO_4 . The solids were filtered and the solvent evaporated to give a crude oil, which was purified by flash chromatography. The title compound was obtained as a yellow oil (0.58g).
 30 NMR (CDCl_3) δ (ppm) 7.68 (m, 1H), 6.98 (m, 2H), 2.56-2.52 (2s, 6H).
 35 IR (Film) (cm^{-1}) 1712, 1674.

5-(4-Fluoro-2-methyl-phenyl)-6-methyl-2,3-dihydro-pyrazin

To a solution of intermediate 42 (0.58g) and ethylene diamine (0.22 mL) in toluene (13ml), at r.t., under N_2 , was added anh. Na_2SO_4 (2g). The reaction mixture was heated at reflux for 6 hr. It was then cooled down to r.t. and filtered. The solids were rinsed with CH_2Cl_2 . The solvent was evaporated and the crude oil was purified by flash chromatography. The title compound was obtained as an orange oil (0.44g).

NMR ($CDCl_3$) δ (ppm) 7.18 (m, 1H), 7.0-6.9 (m, 2H), 3.6-3.45 (2m, 4H), 2.20 (s, 3H), 1.88 (t, 3H).

IR (Film) (cm^{-1}) 1612, 1530.

MS (m/z) 204 [M]⁺.

Intermediate 44**2-Methyl-3-phenyl-piperazine-1-carboxylic acid benzyl ester**

To a solution of intermediate 43 (554mg) in anh. MeOH (11ml), under N_2 , at r.t., was added Pd/C 10% (110mg) and the reaction mixture was placed under an H_2 atmosphere for 2 hr. The catalyst was then filtered (filter paper) and rinsed with EtOAc. The solvent was evaporated and the residue dried under vacuum. 2-(4-Fluoro-2-methyl-phenyl)-3-methyl piperazine was obtained as a yellow oil (565mg) and was dissolved in anh. CH_2Cl_2 (27ml), at -5°C, under N_2 . To this solution were added Et₃N (549 μ L) and CBZ-Cl (426 μ L). The solution was stirred at -5°C for 2 hr. It was then poured in sat.aq. $NaHCO_3/CH_2Cl_2$ and the phases were separated. The aqueous layer was extracted with CH_2Cl_2 (1x) and the combined organic extracts were dried over Na_2SO_4 . The solids were filtered and the solvent evaporated. The crude oil was purified by flash chromatography. The title compound was obtained as a yellow oil (111mg).

NMR ($CDCl_3$) δ (ppm) 7.45-7.36 (m, 6H), 6.86 (m, 2H), 5.17 (m, 2H), 4.48-4.36 (m, 1H), 4.09-4.04 (2d, 1H), 4.05-3.94 (2bd, 1H), 3.25-2.88 (m, 3H), 2.40 + 2.28 (2s, 3H), 0.97 + 0.96 (2d, 3H).

IR (Film) (cm^{-1}) 1688.

MS (m/z) 343 [MH]⁺.

35

Intermediate 45

4-[(3,5-Bis-trifluoromethyl-benzyl)-methyl-carbamoyl]-3-(4-fluoro-2-methyl-phenyl)-2-methyl-piperazine-1-carboxylic acid benzyl ester

To a solution of intermediate 44 (358mg) in anh. CH_2Cl_2 (15ml), at 0°C, under N_2 , was added triethylamine (292 μL). To this solution was added a solution of triphosgene (140 mg) in anh. CH_2Cl_2 (6ml). The reaction mixture was stirred at 0°C for 2 hr.

To this solution were added iPr_2NEt (181 μL) and N-methyl-bis(trifluoromethyl)benzylamine hydrochloride (370mg). The solution was stirred at r.t. for 18 hr. It was then diluted with CH_2Cl_2 , washed with 10% citric acid (1x) and dried over Na_2SO_4 . The solids were filtered, the solvent was evaporated and the crude oil purified by flash chromatography. The title compound was obtained (545mg) as a white foamy solid.

NMR (CDCl_3) δ (ppm) 7.76 (s, 1H), 7.50 (s, 2H), 7.34-7.30 (m, 5H), 7.00 (m, 1H), 6.85 (m, 1H), 6.76 (m, 1H), 5.2-5.1 (dd, 2H), 4.75 (d, 1H), 4.30 (d, 1H), 4.65 (m, 1H), 4.35 (m, 1H), 4.00 (m, 1H), 3.54-3.40 (m, 2H), 3.1 (m, 1H), 3.06 (s, 3H), 2.38 (s, 3H), 1.05 (d, 3H).

IR (Film) (cm^{-1}) 3437, 1705, 1664.

MS (m/z) 626 [MH^+].

20

Intermediate 46

3-(2-Methyl-4-fluoro-phenyl)-5-Methyl-5,6 dihydro-1H-pyrazin-2-one

under inert atmosphere Intermediate 23 (0.2g) was dissolved in dry toluene (5ml), then 1,2 diamino propane (0.102ml) was added drop-wise followed by Na_2SO_4 (0.2g) and the reaction mixture was refluxed for 2 hr; the solids were filtered off and the crude product obtained after evaporation of the solvent was purified by flash chromatography affording the title compound in a mixture with 3-(2-Methyl-4-fluoro-phenyl)-6-Methyl-5,6 dihydro-1H-pyrazin-2-one (0.200g).

$^1\text{H-NMR}$ (DMSO) δ (ppm) 8.42 (bs, 1H), 7.24 (m, 1H), 7.02 (m, 2H), 3.85 (m, 1H), 3.40 (dt, 1H), 3.13 (t, 1H), 2.18 (s, 3H), 1.25 (d, 3H).

IR (Nujol) (cm^{-1}) 3450, 1682, 1614. MS (m/z) 221 [MH^+].

35

Interm diat 47

3-(2-M thyl-4-fluoro-phenyl)-5-M thyl-piperazin-2-one (mixture of syn enantiomers)

Intermediate 46 (0.180g) was dissolved in MeOH (4ml) and Pd/C 10% (36mg) was added. After 2 hr the reduction was complete. The reaction mixture was filtered on a celite pad, the solvent was removed under reduced pressure and the crude product purified by flash-chromatography, affording a 9:1 mixture of the title compound and the anti enantiomers (0.110g).

¹H-NMR (DMSO) δ (ppm) 7.88 (s, 1H), 7.07-6.92 (m, 3H), 4.48 (s, 1H), 3.3 (m, 1H), 2.91 (m, 2H), 2.65 (bs, 1H), 2.34 (s, 3H), 0.95 (d, 3H).

IR (Nujol) (cm⁻¹) 3441, 3285, 1675.

MS (m/z): 223 [MH]⁺.

Intermediate 48

2-(2-Methyl-4-fluoro-phenyl)-3-oxo-piperazine-6-Methyl-1-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide; mixture of syn enantiomers

To a solution of intermediate 47 (0.105g) and triethylamine (0.197ml) in dry CH₂Cl₂ (5ml) was added drop-wise, at 0°C, a solution of triphosgene (0.056g) in dry CH₂Cl₂ (3ml) under inert atmosphere. The temperature was maintained at 0°C for 3 hr, before the addition of diisopropylethylamine (0.3ml) followed by 3,5-bistrifluoromethyl-methylamine hydrochloride (0.166g). The reaction mixture was stirred at room temperature overnight before being diluted with CH₂Cl₂ and washed with a 1N solution of HCl, H₂O and brine in sequence. The organic phase was dried on Na₂SO₄ and the crude product obtained after evaporation of the solvent was purified by flash column chromatography affording the title compound as a foam (0.085g).

¹H NMR (DMSO) δ (ppm) 8.08 (bt, 1H), 7.95 (s, 1H), 7.63 (s, 2H), 7.13 (t, 1H), 6.87 (d, 1H), 6.79 (t, 1H), 5.21 (s, 1H), 4.51 (dd, 2H), 3.64 (m, 1H), 3.30 (m, 1H), 3.18 (m, 1H), 2.77 (s, 3H), 2.25 (s, 3H), 1.20 (d, 3H).

IR (Nujol) (cm⁻¹) 1675.

MS (m/z): 506 [MH]⁺.

35 Example 1

2-(4-fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid (3,5-bistrifluoro-methyl-benzyl)-methyl-amide; hydrochloride

5 A solution of intermediate 13 (0.05g) in EtOH (10ml) was hydrogenated at atmospheric pressure for 3 hr, in the presence of 10% Pd/C (10mg) as catalyst. The catalyst was filtered off and the solvent was evaporated. The crude residue dissolved in diethyl ether and then a 1M sol. of HCl in diethyl ether (0.1ml) was added. The formed precipitate was filtered and washed with diethyl ether to obtain the title compound (0.02g) as a white 10 powder.

m.p. > 220°C

15 NMR (DMSO) δ (ppm) 9.33 (bm, 1H), 9.18 (bm, 1H), 7.96 (s, 1H), 7.59 (s, 2H), 7.33 (dd, 1H), 6.99 (d, 1H), 6.85 (t, 1H), 4.63 (d, 1H), 4.53 (d, 1H), 4.37 (d, 1H), 3.52 (d, 1H), 3.4-3.2 (m, 2H), 3.25 (m, 1H), 3.04 (t, 1H), 3.0-2.8 (m, 1H), 2.93 (s, 3H), 2.38 (s, 3H).

IR (Nujol) (cm⁻¹) 3200, 1659

MS (m/z) 478 [M-Cl]⁺

Example 2

20 2-(3-Isopropyl-phenyl)-piperazine-1-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide; hydrochloride

25 To a solution of intermediate 14 (0.353g) in anh. EtOH (5.7 mL), at r.t., under N₂, Pd/C 10% (175mg, 50% wt) was added. The black suspension was placed under an atmosphere of H₂ and was stirred for 3 hr. The catalyst was then filtered on Celite and the Celite cake was rinsed with EtOH. HCl 1.0M/Et₂O was then added (1.13 mL). The solvent was evaporated and the oil obtained was triturated with Et₂O. The solid was filtered, rinsed with Et₂O and dried under vacuum. The title compound was obtained as a grey solid (104mg).

30 m.p. 77-80°C

NMR (CDCl₃): δ (ppm) 8.95 (bs, 2H), 7.97 (s, 1H), 7.75 (s, 1H), 7.22-7.08 (m, 4H), 4.58-4.41 (2d, 2H), 4.50 (dd, 1H), 3.44 (m, 1H), 3.4-3.1 (m, 5H), 2.84 (s, 3H), 2.80 (m, 1H), 1.12 (d, 3H), 1.07 (d, 3H).

IR (Nujol) (cm⁻¹) 3437, 1653

35 MS (m/z) 488 [M-Cl]⁺

Example 3**2-(2-Isopropyl-phenyl)-piperazine-1-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide; hydrochloride.**

5 To a solution of intermediate 15 (0.108g) in anh. EtOH (2.0 mL), at r.t., under N_2 , Pd/C 10% (20mg, 20% wt) was added. The black suspension was placed under an atmosphere of H_2 and was stirred for 3 hr. The catalyst was then filtered on Celite and the Celite cake was rinsed with EtOH. HCl 1.0M/Et₂O was then added (350 μ L). The solvent was evaporated and the oil obtained was triturated with Et₂O. The solid was 10 filtered, rinsed with Et₂O and dried under vacuum. The title compound was obtained as a brown solid (29mg).

m.p. 108-110°C

15 NMR (CDCl₃): δ (ppm) 9.15 (bd, 1H), 8.92 (bd, 1H), 7.97 (s, 1H), 7.66 (s, 2H), 7.30 (m, 1H), 7.27 (m, 1H), 7.19 (dt, 1H), 7.03 (dt, 1H), 4.69 (dd, 1H), 4.55 (2d, 2H), 3.53 (m, 1H), 3.39 (m, 3H), 3.19 (bd, 1H), 3.04 (dt, 1H), 2.92 (m, 4H), 1.24 (d, 3H), 1.20 (d, 3H).

IR (Nujol) (cm⁻¹) 3441, 1662.

MS (m/z) 489 [M-Cl]⁺.

20 **Example 4**

2-(4-Fluoro-3-methyl-phenyl)-piperazine-1-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide; hydrochloride.

25 To a solution of intermediate 16 (0.226g) in anh. EtOH (3.7 mL), at r.t., under N_2 , Pd/C 10% (23 mg, 10% wt) was added. The black suspension was placed under an atmosphere of H_2 and stirred for 3 hr. The catalyst was then filtered on Celite and the Celite cake was rinsed with EtOH. HCl 1.0M/Et₂O was then added (740 μ L). The solvent was evaporated and the oil obtained was triturated with Et₂O. The solid was filtered, rinsed with Et₂O and dried under vacuum. The title compound was obtained as a white solid (112mg).

30 m.p. 70-72°C

NMR (CDCl₃): δ (ppm) 9.08 (m, 2H), 7.97 (s, 1H), 7.67 (s, 2H), 7.19 (m, 1H), 7.14 (m, 1H), 7.01 (t, 1H), 4.59 (d, 1H), 4.43 (m, 1H), 4.40 (d, 1H), 3.1-3.5 (m, 6H), 2.92 (s, 3H), 2.14 (s, 3H).

35 IR (Nujol) (cm⁻¹) 3406, 1653

MS (m/z) 478 [M-Cl]⁺

Example 5**2-(2,4-Difluoro-phenyl)-piperazine-1-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide; hydrochloride**

5 To a solution of intermediate 17 (0.134g) in anh. EtOH (2.0 mL), at r.t., under N₂, Pd/C 10% (27mg, 20% wt) was added. The black suspension was placed under an atmosphere of H₂ and was stirred for 3 hr. The catalyst was then filtered on Celite and the Celite cake was rinsed with EtOH. HCl 1.0M/Et₂O was then added (436 μ L). The solvent was evaporated and the oil obtained was triturated with Et₂O. The solid was filtered, rinsed with Et₂O and dried under vacuum. The title compound was obtained as a yellow solid (112mg).
m.p. 220-230°C
NMR (CDCl₃): δ (ppm) 9.08-9.3 (m, 2H), 7.97 (s, 1H), 7.62 (s, 2H), 7.44 (m, 1H), 7.18 (m, 1H), 6.95 (m, 1H), 4.65 (m, 1H), 4.3-4.65 (dd, 2H), 3.2-3.6 (m, 4H), 3.07 (m, 2H), 2.92 (s, 3H).
IR (Nujol) (cm⁻¹) 3400, 1656
MS (m/z) 482 [M-Cl]⁺.

10

20 **Example 6**

2-(4-fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-amide; hydrochloride

A solution of intermediate 18 (0.086g) in EtOH (10ml) was hydrogenated at atmospheric pressure for 2 hr, in the presence of 10% Pd/C (20mg) as catalyst. The catalyst was filtered off and the solvent was evaporated. The crude residue dissolved in diethyl ether and then a 1M sol. of HCl in diethyl ether (0.1ml) was added. The solvent was evaporated to obtain the title compound (0.05g) as a white solid.
NMR (DMSO) δ (ppm) 9.06 (m, 1H), 8.88 (m, 1H), 7.91 (s, 1H), 7.77 (s, 2H), 7.42 (t, 1H), 7.22 (dd, 1H), 7.03 (m, 1H), 6.94 (t, 1H), 5.22 (t, 1H), 4.34 (m, 2H), 3.98 (m, 1H), 3.64 (m, 1H), 3.4-3.2 (m, 2H), 3.22 (m, 2H), 2.32 (s, 3H).
IR (Nujol) (cm⁻¹) 3360, 1645
MS (m/z) 464 [M-Cl]⁺.

25

30

35

Example 7

(+)-2-(4-fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide hydrochloride

A solution of intermediate 20a (0.120g) in EtOH (5ml) was hydrogenated at atmospheric pressure for 4 hr, in the presence of 10% Pd/C (25mg).

5 Then the catalyst was filtered off and the solvent was evaporated. The crude product was dissolved in diethyl ether and then a solution 1M of HCl in diethyl ether (0.3ml) was added. Then the precipitate was filtered and washed with diethyl ether to obtain the title compound (0.057g) as a white solid.

10 m.p.>220°C

NMR (DMSO) δ (ppm) 9.11 (m, 1H); 8.83 (m, 1H); 7.96 (s, 1H); 7.59 (s, 2H); 7.34 (dd, 1H); 6.94 (dd, 1H); 6.86 (m, 1H); 4.65-4.35 (dd, 2H); 4.49 (m, 1H); 3.54 (m, 1H); 3.44-3.01(m, 4H); 2.93 (s, 3H); 2.90 (m, 1H); 2.38 (s, 3H).

15 MS (m/z) 479 [MH-Cl]⁺

$[\alpha]_D^{20} = +69.5$ C = 0.27(g/100ml) CHCl₃

Example 8

Method A

20 **(-)-2-(4-fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide hydrochloride**

A solution of intermediate 20b (0.110g) in EtOH (5ml) was hydrogenated at atmospheric pressure for 4 hr, in the presence of 10% Pd/C (25mg).

25 Then the catalyst was filtered off and the solvent was evaporated. The crude product was dissolved in diethyl ether and then a solution 1M of HCl in diethyl ether (0.3ml) was added. Then the precipitate was filtered and washed with diethyl ether to obtain the title compound (0.045g) as a white solid.

Method B

30 **(-)-2-(4-fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid (3,5-bistrifluoro methyl-benzyl)-methyl-amide; hydrochloride**

A solution of intermediate 37a (0.24g) in EtOH (4ml) was hydrogenated at atmospheric pressure for 3 hr, in the presence of 10% Pd/C (73mg) as catalyst. The catalyst was filtered off and the solvent was evaporated.

35 The crude residue dissolved in diethyl ether and then a 1M sol. of HCl in diethyl ether (0.58ml) was added. The formed precipitate was filtered and

washed with diethyl ether to obtain the title compound (0.04g) as a white powder.

Method C

To Intermediate 39 (2.37g) triethylamine (3.15ml) in dry CH_2Cl_2 (57ml) 5 was added drop-wise, at 0°C. Then a solution of triphosgene (1.502g) in dry CH_2Cl_2 (12ml) under inert atmosphere was added. The temperature was maintained at 0°C for 3 hr, before the addition of diisopropylethylamine (4ml) followed by 3,5-bis-trifluoromethylbenzyl-N- 10 methyl amine (4.62g) in acetonitrile (142ml). The reaction mixture was heated to reflux for 3 hr then cooled to room temperature diluted with CH_2Cl_2 (25ml) and washed with a 1N solution of HCl (25ml), H_2O (25ml) and brine (25ml) in sequence. The organic phase was dried on Na_2SO_4 (2g) and the crude product obtained after evaporation of the solvent was purified by flash column chromatography (from Ethyl 15 Acetate/Cyclohexane 4/1 to pure Ethyl Acetate) to give 2-(4-Fluoro-2-methyl-phenyl)-3-oxo-piperazine-1-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide as a foam (1.79g). This compound was reduced with $\text{BH}_3\text{-THF}$ (17.6ml) following the standard procedure (4 hr reflux in 10ml of THF, then work-up with 6ml of 20 HCl 37% and subsequent neutralisation with 5g of solid NaHCO_3) to give the title compound (1.16g).

m.p.>220°C

NMR (DMSO) δ (ppm) 9.11 (m, 1H); 8.83 (m, 1H); 7.96 (s, 1H); 7.59 (s, 2H); 7.34 (dd, 1H); 6.94 (dd, 1H); 6.86 (m, 1H); 4.65-4.35 (dd, 2H); 4.49 (m, 1H); 3.54 (m, 1H); 3.44-3.01(m, 4H); 2.93 (s, 3H); 2.90 (m, 1H); 2.38 (s, 3H).

MS (*m/z*) 479 [MH-Cl]⁺

$[\alpha]_D^{20} = -72.6$ C = 0.27(g/100ml) CHCl_3

30 **Example 9**

2-(4-fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid [1-(3,5-bis-trifluoromethyl-phenyl)ethyl]-methyl-amide;hydrochloride (mixture of the enantiomers A,B)

A solution of intermediate 22a (0.05g) in EtOH (5ml) was hydrogenated at 35 atmospheric pressure for 1 1/2 hr, in the presence of 10% Pd/C (15mg). Then the catalyst was filt red off and the solvent was evaporated. Th

crude product was dissolved in diethyl ether and then a solution 1M of HCl in diethyl ether (0.5ml) was added. Then the precipitate was filtered and washed with diethyl ether to obtain the title compound (0.025g) as a white powder.

5 NMR (CDCl₃) δ (ppm) 10.2 (b, 1H); 7.78 (s, 1H); 7.54 (s, 2H); 7.13 (dd, 1H); 6.88 (dd, 1H); 6.82 (m, 1H); 5.48 (q, 1H); 4.57 (m, 1H); 3.6-3.5 (m, 2H); 3.38 (m, 2H); 3.3-3.0 (m, 2H); 2.71 (s, 3H); 2.48 (s, 3H); 1.44 (d, 3H).
IR(CDCl₃) 1663
10 MS (m/z) 491 [M-Cl]⁺

Example 10

2-(4-fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid [1-(3,5-bis-trifluoromethyl-phenyl)ethyl]-methyl-amide; hydrochloride (mixture of the enantiomers C,D)

15 A solution of intermediate 22b (0.05g) in EtOH (5ml) was hydrogenated at atmospheric pressure for 1 ½ hr, in the presence of 10% Pd/C (15mg). Then the catalyst was filtered off and the solvent was evaporated. The crude product was dissolved in diethyl ether and then a solution 1M of HCl in diethyl ether (0.5ml) was added. Then the precipitate was filtered and washed with diethyl ether to the title compound (0.057g) as a white powder.

20 NMR (CDCl₃) δ (ppm) 10.2 (b, 1H); 7.74 (s, 1H); 7.41 (s, 2H); 7.10 (m, 1H); 6.88 (m, 1H); 6.80 (m, 1H); 5.58 (q, 1H); 4.85 (m, 1H); 3.7-2.9 (m, 6H); 2.80 (s, 3H); 2.49 (s, 3H); 1.44 (d, 3H).
25 IR (CDCl₃) 1662
MS (m/z) 491 [M-Cl]⁺

Example 11

2-(4-Fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide

30 To a solution of intermediate 32 (813mg) in anh. THF (6.6 mL), at r.t., under N₂, BH₃·THF 1M/THF (9.9 mL) was added. The solution was heated at reflux for 3 hr. It was then brought back to r.t. and 1N HCl (4 mL) was added slowly in order to destroy the borane complexes. The reaction mixture was stirred at r.t. for 18 hr. The THF was evaporated

and the aqueous phase was basified with 10% NaOH. It was then extracted with EtOAc (3x). The combined organic extracts were dried over Na₂SO₄, the solids were filtered and the solvent evaporated. The title compound was used as such in the next step (790mg).

5 NMR (CDCl₃): δ (ppm) 7.77 (s, 1H), 7.49 (s, 2H), 7.33 (m, 1H), 6.86 (m, 1H), 6.82 (m, 1H), 4.65-4.46 (2d (AB), 2H), 4.46 (m, 1H), 3.40-2.85 (m, 6H), 2.97 (s, 3H), 2.66 (s, 3H).
IR (CDCl₃; cm⁻¹): 1653.
MS (m/z): 478 [MH]⁺

10

Example 12

2-(4-Fluoro-phenyl)- piperazine-1-carboxylic acid (3,4-bis-trifluoromethyl-benzyl)-methyl-amide; hydrochloride.

15 Intermediate 33 (0.180g) was dissolved in dry THF (8ml) under inert atmosphere; BH₃.THF complex (1.88ml) was added very carefully and the reaction mixture was refluxed 3 hr. After completion of the reduction HCl 37% was added (3ml) and the reaction mixture was refluxed 2 hr. THF was removed under reduced pressure, water was added (3ml) and the aqueous solution was basified by means of Na₂CO₃, extracted with CH₂Cl₂, washed with brine and dried on Na₂SO₄. The crude product was purified by flash chromatography (silica gel, 8:2 EtOAc/MeOH) affording the free amine which was treated with a 1M solution of HCl in Et₂O (0.3ml) to yield the title compound (0.05g) as a white solid.
mp > 200°C

20 25 NMR (DMSO) δ (ppm): 9.08 (bs, 2H), 7.97 (s, 1H), 7.66 (s, 2H), 7.35 (m, 2H), 7.10 (m, 2H), 4.60 (d, 1H), 4.46 (dd, 1H), 4.39 (d, 1H), 3.50-3.10 (m, 6H), 2.92 (s, 3H).
IR (Nujol) (cm⁻¹) 3437, 1653
MS: 464 [M-Cl]⁺.

30

Example 13

2-Phenyl-piperazine-1-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl- amide; hydrochloride.

35 To a stirred solution of intermediate 34 (0.382g) in THF (10ml) a 1M solution of BH₃ in THF (1.66ml) was added. The mixture was then refluxed for 3 hr. The temperature was then cooled, and the reaction was quenched with a solution of HCl 37% (5ml) and stirred at room

temperature overnight. The solution was then basified with NaOH and the product was extracted with CH_2Cl_2 , dried (Na_2SO_4) and concentrated under reduced pressure to give an oil. The oil was then dissolved in Et_2O and a 1M solution of HCl in Et_2O (1.6ml) was added. After a few minutes the solution was concentrated, and the product was triturated from petroleum ether to give the title compound (0.300g) as a solid.

5 $\text{NMR}(\text{CDCl}_3)$: δ (ppm): 10.15(b, 2H); 7.75(s, 1H); 7.44(s, 2H); 7.3(m, 5H); 4.80-4.34(m, 3H); 3.80-3.00(m, 6H); 2.93(s, 3H)
10 MS (m/z): 446 [M-Cl]⁺.

Example 14

2-(2,4-dichloro-phenyl)-piperazine-1-carboxylic acid (3,5-bistrifluoro methyl-benzyl)-methyl-amide hydrochloride.

To a solution of intermediate 35 (0.22g) in THF (15ml) a 1M solution of borane in THF (1.2ml) was added and the reaction mixture was stirred at reflux for 3 hr, then cooled to r.t. 37% HCl (3ml) was added drop-wise and the reaction mixture stirred for 3 hr. The solvent was evaporated and the crude residue was diluted with ethyl acetate and washed with a saturated solution of NaHCO_3 and brine. The organic phase was next dried with Na_2SO_4 and concentrated to give the crude product. The latter was dissolved in diethyl ether (2ml), then a 1M sol of HCl in diethyl ether (1ml) was added. The obtained solution was added drop-wise in petroleum (30ml) and the formed precipitate was filtered to obtain the title compound (0.06g, white solid).

15 25 NMR (DMSO) δ (ppm) 9.25, 9.15 (m+m, 2H), 7.98 (m, 1H), 7.64 (s, 2H), 7.60 (d, 1H), 7.45 (d, 1H), 7.29 (dd, 1H), 4.78 (dd, 1H), 4.63 (d, 1H), 4.35 (d, 1H), 3.59 (d, 1H), 3.40-3.25 (m, 3H), 3.07 (t, 3H), 2.95, 2.93 (s+m, 4H).

30 IR (Nujol) (cm^{-1}) 3442, 1654

MS (m/z) 515 [M-Cl]⁺.

Example 15

2-(3,4-dichloro-phenyl)-piperazine-1-carboxylic acid (3,5-bistrifluoro m thyl-b nzyl)-m thyl-amide; hydrochloride.

35 To a solution of intermediate 36 (0.13g) in THF (20ml) a 1M solution of borane in THF (1.96ml) was added and the reaction mixture was stirred

at reflux for 3 hr, then cooled to r.t. 37% HCl (5ml) was added drop-wise and the reaction mixture was stirred for 3 hr. The solvent was evaporated and the crude residue was diluted with ethyl acetate and washed with a saturated solution of NaHCO₃ and brine. The organic phase was next dried with Na₂SO₄ and concentrated to give the crude product. The latter was dissolved in diethyl ether (2ml), then a 1M sol of HCl in diethyl ether (1ml) was added. The obtained solution was added drop-wise in petroleum (30ml) and the formed precipitate was filtered to obtain the title compound (0.016g, white solid).

5 NMR (DMSO) δ (ppm) 8.99 (broad, 2H), 7.98 (s, 1H), 7.70 (s, 2H), 7.56 (d+d, 2H), 7.31 (dd, 1H), 4.58 (d, 1H), 4.50 (d, 1H), 4.41 (d, 1H), 3.5-3.1 (m, 4H), 2.93 (s, 3H).
 10 IR (Nujol) (cm⁻¹) 3436, 1653
 MS (m/z) 515 [M-Cl]⁺.

15

Example 16
(-)-2-(4-fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid [1-(3,5-bis-trifluoromethyl-phenyl)ethyl]-methyl-amide: hydrochloride (Enantiomer A)

20 A solution of intermediate 38a (0.08g) in EtOH (5ml) was hydrogenated at atmospheric pressure for 4 hr, in presence of 10% Pd/C (50mg). The catalyst was filtered off and the solvent was evaporated. The crude product was dissolved in diethyl ether and then a solution 1M of HCl in diethyl ether (0.5ml) was added. The precipitate was filtered and washed with diethyl ether to obtain the title compound (0.023g).

25 NMR (CDCl₃) δ (ppm) 10.5-10.0 (b, 2H); 7.74 (s, 1H); 7.41 (s, 2H); 7.09 (m, 1H); 6.88 (m, 1H); 6.80 (m, 1H); 5.58 (q, 1H); 4.85 (m, 1H); 3.80-3.00 (m, 6H); 2.80 (s, 3H); 2.49 (s, 3H); 1.53 (d, 3H).
 MS (m/z) 492

30 [α]^D₂₀ = -164.9, 0.12(g/100ml) CHCl₃

Example 17
(+)-2-(4-fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid [1-(3,5-bis-trifluoromethyl-phenyl)ethyl]-methyl-amide: hydrochloride (Enantiomer B)

35

A solution of intermediate 38 b (0.08g) in EtOH (5ml) was hydrogenated at atmospheric pressure for 4 hr, in presence of 10% Pd/C (50mg). The catalyst was filtered off and the solvent was evaporated. The crude product was dissolved in diethyl ether and then a solution 1M of HCl in diethyl ether (0.5ml) was added. The precipitate was filtered and washed with diethyl ether to obtain the title compound (0.020g).

NMR (CDCl₃) δ (ppm) 10.5-10.0 (b, 2H); 7.74 (s, 1H); 7.41 (s, 2H); 7.09 (m, 1H); 6.88 (m, 1H); 6.80 (m, 1H); 5.58 (q, 1H); 4.85 (m, 1H); 3.80-3.00 (m, 6H); 2.80 (s, 3H); 2.49 (s, 3H); 1.53 (d, 3H).

MS (m/z) 492

[α]^D₂₀ = +207, 0.11 (g/100ml) CHCl₃

Example 18

2-(4-Fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid [1-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methyl- amide; acetate salt (enantiomerC)

To a solution of intermediate 40a (8.8g) in dry THF (33ml) under N₂ BH₃.THF (1M solution in THF 87ml) was added and the reaction mixture was stirred at reflux for 3 hr, then cooled to r.t. and HCl (37%, 30 ml) was added drop-wise maintaining the reaction mixture in an ice-bath. The reaction mixture was stirred at r.t. for 1 hr. Water was then added (70ml) and solid NaHCO₃ (35.2g) was added portionwise until a pH of 6.5. The THF was evaporated and the aqueous phase was extracted with Et₂O (3x88ml). The combined organic phases were dried (Na₂SO₄), and evaporated to leave a colourless oil (7.37g).

This crude oil was purified by flash chromatography (silica gel EtOAc/Methanol 7/3). The product obtained was suspended in Et₂O (125ml) and washed with NaHCO₃ sat. (2x20ml). The clear combined organic phases were dried on Na₂SO₄ and evaporated to obtain the title compound as white foam (5.27gr).

NMR (¹H, DMSO-d₆): δ 7.98 (s, 1H), 7.70 (s, 2H), 7.87 (m, 1H), 6.91 (m, 1H), 6.77 (m, 1H), 5.29 (q, 1H), 4.23 (dd, 1H), 3.2-2.6 (m, 6H), 2.68 (s, 3H), 2.3 (s, 3H), 1.89 (s, 3H), 1.48 (d, 3H).

MS (m/z): 492 [M-CH₃COO]⁺.

[α]^D = - 120.4°C Solvent (CHCl₃); Source:Na; Cell volume [mL]: 1; Cell pathlength [dm]: 1; Cell temperature [°C]: 20; Wavelength [nm]: 589

Example 19**2-(4-Fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid [1-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methyl- -amide; acetate salt (enantiomer A)**

5 To a solution of intermediate 40b (2.57g) in dry THF (15.5ml), at 0°C, under N₂, was added BH₃·THF (1M solution in THF) then heated at reflux for 3 hr. It was then brought back to r.t. and HCl 37% (9ml) was added slowly maintaining the reaction mixture in an ice-bath. The
10 reaction mixture was stirred at r.t. for 1 hr. Water was then added (20.5ml) and solid NaHCO₃ (10.3g) was added portionwise until a pH of 7.

15 The THF was evaporated and the aqueous phase was extracted with Et₂O (3x25.7ml). The combined organic phases were dried (Na₂SO₄), and evaporated to leave a yellow oil (2.34g). This crude oil was dissolved in Et₂O (35ml) and glacial AcOH (0.245ml) was added drop-wise. The mixture was stirred 2 hr at 0°C, then it was filtered, washed with Et₂O (10ml) and dried under vacuum to obtain the title compound as a white solid (1.349gr).

20 **NMR (¹H, DMSO-d₆):** δ 7.92 (s, 1H), 7.58 (s, 1H), 7.29 (m, 1H), 6.90 (m, 1H), 6.77 (m, 1H), 5.33 (q, 1H), 4.19 (m, 1H), 3.2-2.6 (m, 6H), 2.79 (s, 3H), 2.32 (s, 3H), 1.89 (s, 3H), 1.48 (d, 3H).

MS (m/z): 492 [M-CH₃COO]⁺.

[α]^D = +2.2 °C

25 **Solvent** (CHCl₃); **Source:Na**; **Cell volume [mL]**: 1; **Cell pathlength [dm]**: 1; **Cell temperature [°C]**: 20; **Wavelength [nm]**: 589

Example 20**4-(2-Amino-acetyl)-2-(4-fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid(3,5-bis-trifluoromethyl-benzyl)-methyl-amide, hydrochloride**

30 **Example 8** (0.05g) was dissolved in dry DMF (2ml), diisopropylethylamine (0.019ml) was added and the solution thus obtained was added to a solution of N-(tert-butoxycarbonyl)glycine (0.0192g), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (0.0214g) and 1-hydroxybenzotriazole (0.015g) in dry DMF (5ml). The reaction mixture was stirred 18hr at room temperature, then diluted with ethyl acetate

(30ml), washed with water (30ml), sodium bicarbonate (30ml) and brine (30ml). The separated organic layer was dried on sodium sulphate, filtered and evaporated and the crude was then chromatographed (silica gel, 100% EtOAc) to give a product (0.043g) which was dissolved in a 5 1M solution of HCl in diethylether (5ml), stirred 0.5 hr at room temperature and evaporated to obtain the title compound (0.046g) as a yellow foam.

10 NMR (DMSO) δ (ppm) 8.01 (bs, 3H), 7.88 (s, 1H), 7.67 (s, 2H), 7.33 (m, 1H), 6.95 (m, 1H), 6.83 (m, 1H), 4.60 (m, 1H), 4.60-4.42 (dd, 2H), 4.2-3.3 (m, 6H), 3.2 (m, 2H), 2.89 (s, 3H), 2.4 (s, 3H).

15 IR (Nujol) (cm^{-1}) 3410, 1660.

MS (m/z) 535 [M-Cl]⁺.

Example 21

15 2-(4-fluoro-2-methyl-phenyl)-4-(piperidine-4-carbonyl)-piperazine-1-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide, hydrochloride

20 Example 8 (0.05g) was dissolved in dry DMF (2ml), diisopropylethylamine (0.019ml) was added and the solution thus obtained was added to a solution of piperidine-1,4-dicarboxylic acid mono-tert-butyl ester (0.0192g), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (0.025g) and 1-hydroxybenzotriazole (0.015g) in dry DMF (5ml). The reaction mixture was stirred 18 hr at room temperature, then diluted with ethyl acetate (30ml), washed with water (30ml), sodium bicarbonate (30ml) and brine (30ml). The separated organic layer was dried on sodium sulphate, filtered and evaporated. The crude was then chromatographed (silica gel, 9:1 EtOAc/MeOH) to give a product (0.040g) which was dissolved in a 1M solution of HCl in diethylether (5ml), stirred 25 0.5 hr at room temperature and evaporated to obtain the title compound (0.043g) as a yellow foam.

30 NMR (DMSO) δ (ppm) 8.71 (bs, 1H), 8.38 (bs, 1H), 7.86 (s, 1H), 7.66 (s, 2H), 7.31 (m, 1H), 6.95 (m, 1H), 6.83 (m, 1H), 4.55 (m, 1H), 4.60-4.43 (dd, 2H), 3.9-3.4 (m, 7H), 2.8-2.7 (m, 8H), 2.88 (s, 3H), 2.37 (s, 3H).

35 IR (Nujol) (cm^{-1}) 3401, 1639.

MS (m/z) 589 [M-Cl]⁺.

Example 22**4-(2-Amino-ethyl)-2-(4-fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide, dihydrochloride salt**

5 To a solution of intermediate 41 (25mg) in absolute EtOH (1mL), at room temperature, was added methylamine 8.03M/EtOH (48 μ L). The reaction mixture was stirred at r.t. for 5 hr. The solvent was evaporated and the crude product purified by flash chromatography (silica gel, 90:5:5 EtOAc/MeOH/NH₄OH conc.). The fractions were collected and the solvent was evaporated. The residue was dissolved in Et₂O and HCl 1.0M/Et₂O (150 μ L) was added. The yellow precipitate was filtered and dried to give the title compound (19mg) as a yellow solid.

10 NMR (DMSO) δ (ppm) 8.12 (bs, 2H), 7.90 (s, 1H), 7.62 (s, 2H), 7.33 (t, 1H), 6.95 (dd, 1H), 6.83 (td, 1H), 4.69 (m, 1H), 4.62 (d, 1H), 4.41 (d, 1H), 15 3.60-3.10 (m, 10H), 2.94 (s, 3H), 2.40 (s, 3H).
IR (Nujol) (cm⁻¹) 3433 – 3300, 1651.
MS (m/z) 521 [M-2HCl+H]⁺.

Example 23**2-(4-Fluoro-2-methyl-phenyl)-3-methyl-piperazine-1-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide, hydrochloride salt**

20 To a solution of intermediate 45 (100mg) in anh. MeOH (3ml), under N₂, at room temperature, was added Pd/C 10% (20mg). The reaction mixture was placed under an H₂ atmosphere and stirred at room temperature for 25 2 hr. The catalyst was filtered on Celite, and the Celite cake was rinsed with EtOAc. The solvent was evaporated and the residue was dissolved in Et₂O. HCl 1.0N/Et₂O (240 μ l) was added and the white precipitate was filtered and rinsed with Et₂O. The title compound was obtained (73mg) as a white solid.

30 NMR (CDCl₃) δ (ppm) 9.31 + 9.01 (m, 2H), 7.99 (s, 1H), 7.70 (s, 2H), 7.02 (m, 2H), 6.78 (m, 1H), 4.63 (d, 1H), 4.7-4.3 (dd, 2H), 3.66 (m, 1H), 3.5-2.9 (m, 4H), 3.05 (s, 3H), 2.34 (s, 3H), 1.09 (d, 3H).
IR (Film) (cm⁻¹) 1659.
MS (m/z) 692 [MH-Cl]⁺.

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Example 24

**2-(2-Methyl-4-Fluoro-phenyl)-6-Methyl- piperazine-1-carboxylic acid
(3,5-bis-trifluoromethyl-benzyl)-methyl-amide, hydrochloride
salt.(mixture of syn enantiomers)**

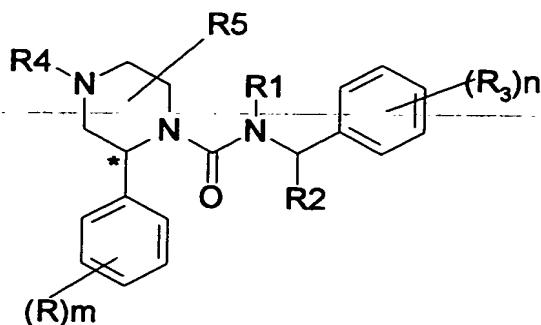
5 Intermediate 47 (0.080g) was dissolved in dry THF (5ml) under inert atmosphere; BH₃·THF complex (1.25ml) was added very carefully and the reaction mixture was refluxed for 3 hr. After completion of the reduction, HCl 37% was added (3ml) and the reaction mixture was refluxed for 2 hr. THF was removed under reduced pressure, water was added (3ml) and the aqueous solution was basified by means of 10 Na₂CO₃, extracted with CH₂Cl₂, washed with brine and dried on Na₂SO₄. The crude product was purified by flash chromatography (silica gel, 8:2 EtOAc/MeOH) affording a product which was dissolved in Et₂O and treated with HCl 1.0M/Et₂O (0.3 mL) affording 0.03g of the title compound.

15 ¹H-NMR (DMSO) δ (ppm) 9.12 (bs, 1H), 8.88 (bs, 1H), 7.93 (s, 1H), 7.56 (s, 2H), 7.37 (m, 1H), 6.74 (m, 2H), 4.71 (d, 1H), 4.35 (dd, 1H), 4.36-4.10 (bm, 1H), 3.35-2.9 (m, 5H), 2.99 (s, 3H), 2.28 (s, 3H), 1.05 (d, 3H).
MS (m/z) 492 [M - Cl]⁺.
mp > 200 °C.

Claims

1. A compound of formula (I)

5



wherein

R represents a halogen atom or a C₁₋₄ alkyl group;

10 R₁ represents hydrogen or a C₁₋₄ alkyl group;

R₂ represents hydrogen or a C₁₋₄ alkyl group;

R₃ represents a trifluoromethyl, a C₁₋₄ alkyl, a C₁₋₄ alkoxy, a trifluoromethoxy or a halogen group;

R₄ represents hydrogen, a (CH₂)_qR₇ or a (CH₂)_rCO(CH₂)_pR₇ group;

15 R₅ represents hydrogen, a C₁₋₄ alkyl or a COR₆ group;

R₆ represents hydrogen, hydroxy, amino, methylamino, dimethylamino, a 5 membered heteroaryl group containing 1 to 3 heteroatoms selected from oxygen, sulphur and nitrogen or a 6 membered heteroaryl group containing 1 to 3 nitrogen atoms;

20 R₇ represents hydrogen, hydroxy, a saturated 5-7 membered heterocyclic group, a 5 membered heteroaryl group containing 1 to 3 heteroatoms selected from oxygen, sulphur and nitrogen a 6 membered heteroaryl group containing 1 to 3 nitrogen atoms or NR₈R₉ wherein R₈ and R₉ represent independently hydrogen or C₁₋₄ alkyl optionally substituted by a hydroxy, amino, by a 5 membered heteroaryl group containing 1 to 3 heteroatoms selected from oxygen, sulphur and nitrogen, by a 6 membered heteroaryl group containing 1 to 3 nitrogen atoms or saturated 5-7 membered heterocyclic or R₈ and R₉ together with the nitrogen atom to which they are attached present a saturated

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5-7 membered heterocyclic group optionally containing an additional heteroatom selected from oxygen, sulphur or nitrogen; m is zero or an integer from 1 to 3; n is zero or an integer from 1 to 3; p or r are zero or an integer from 1 to 4; q is an integer from 1 to 4 and pharmaceutically acceptable salts.

2. 2-(4-fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid [1-(3,5-bis-trifluoromethyl-phenyl)ethyl]-methyl-amide (enantiomer C); and pharmaceutically acceptable salts and solvates thereof.

10 3. 2-(4-fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid [1-(3,5-bis-trifluoromethyl-phenyl)ethyl]-methyl-amide acetate salt. (enantiomer C).

15 4. A compound as claimed in any of claims 1-3 for use in therapy.

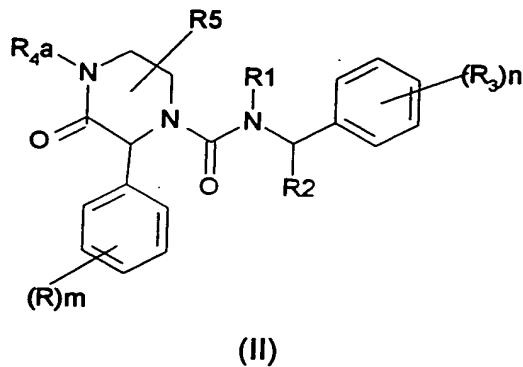
5. The use of a compound as claimed in any of claims 1-3 in the preparation of a medicament for use in the treatment of conditions mediated by tachykinins, including substance P and other neurokinins.

20 6. A pharmaceutical composition comprising a compound as claimed in any of claims 1-3 in admixture with one or more physiologically acceptable carriers or excipients.

25 7. A method for the treatment of a mammal, including man, in particular in the treatment of conditions mediated by tachykinins, including substance P and other neurokinins, comprising administration of an effective amount of a compound claimed in any claims 1 to 3.

30 8. A process (A) for the preparation of a compound of formula (I) as claimed in claim 1, wherein R₄ is hydrogen or a (CH₂)_qR₇ group, provided that when R₅ is a C₁₋₄ alkyl or a COR₆ group, R₅ is not in 3 position of the piperazine ring, which comprises reduction of a compound of formula (II), wherein R_{4a} is hydrogen or a suitable nitrogen protecting group or R_{4a} is a (CH₂)_qR₇ group or protecting derivatives thereof.

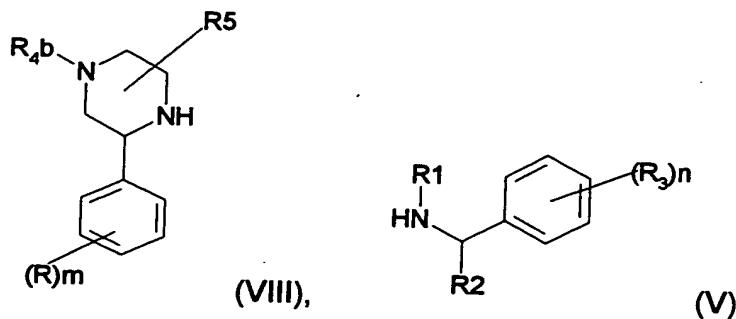
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or

5 a process (B) for the preparation of a compound of formula (I) as claimed in claim 1, wherein R_4 is hydrogen or a $(CH_2)_rCO(CH_2)_pR_7$ group which comprises the reaction of a compound of formula (VIII), wherein R_{4b} represents a nitrogen protecting group or R_{4b} is $(CH_2)_rCO(CH_2)_pR_7$ or a protecting group thereof with triphosgene and an organic base followed by addition of the amine (V)

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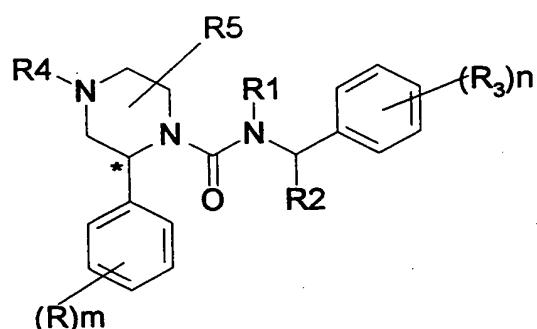
followed where necessary or desired by one or more of the following step:

15 (i) removal of any protecting group;
 (ii) isolation of the compound as salt thereof;
 (iii) separation of a compound of formula (I) or derivative thereof into the enantiomers thereof.

Abstract

The present invention relates to piperazine derivatives of formula (I)

5



wherein

R represents a halogen atom or a C₁₋₄ alkyl group;

R₁ represents hydrogen or a C₁₋₄ alkyl group;

R₂ represents hydrogen or a C₁₋₄ alkyl group;

R₃ represents a trifluoromethyl, a C₁₋₄ alkyl, a C₁₋₄ alkoxy, trifluoromethoxy or an halogen group;

R₄ represents hydrogen, a (CH₂)_qR₇ or a (CH₂)_rCO(CH₂)_pR₇ group;

10 R₅ represents hydrogen, a C₁₋₄ alkyl or a COR₆ group;

R₆ represents hydrogen, hydroxy, amino, methylamino, dimethylamino, a 5 membered heteroaryl group containing 1 to 3 heteroatoms selected from oxygen, sulphur and nitrogen or a 6 membered heteroaryl group containing 1 to 3 nitrogen atoms;

15 R₇ represents hydrogen, hydroxy, a saturated 5-7 membered heterocyclic group, a 5 membered heteroaryl group containing 1 to 3 heteroatoms selected from oxygen, sulphur and nitrogen, a 6 membered heteroaryl group containing 1 to 3 nitrogen atoms or NR₈R₉ wherein R₈ and R₉ represent independently hydrogen or a C₁₋₄ alkyl group

20 optionally substituted by a hydroxy, amino, by a 5 membered heteroaryl group containing 1 to 3 heteroatoms selected from oxygen, sulphur and nitrogen, by a 6 membered heteroaryl group containing 1 to 3 nitrogen atoms or saturated 5-7 membered heterocyclic or R₈ and R₉ together with the nitrogen atom to which they are attached or present a saturated

5

5-7 membered heterocyclic group optionally containing an additional heteroatom selected from oxygen, sulphur or nitrogen; m is zero or an integer from 1 to 3; n is zero or an integer from 1 to 3; p or r are zero or an integer from 1 to 4; q is an integer from 1 to 4 and pharmaceutically acceptable salts; to processes for their preparation and their use in the treatment of conditions mediated by tachykinins.

